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PROPHYLAXIS OF MEASLES WITH CONVALESCENT SERUM

PRINCIPAL FACTORS INFLUENCING THE RESULTS

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The first successful prophylaxis of measles with convalescent serum was reported by Cenci in 1901.[1] The popularity of this method, as indicated by the number of reports in the literature, began about 1920. In Germany many of the studies were conducted by Degkwitz,[2] in France by Debré[3] and in England by Gunn.[4] In the United States the use of the serum was introduced by Park and Zingher[5] in 1916. Additional studies demonstrating the prophylactic effectiveness of measles convalescent serum have been contributed by many workers.[6] A complete review of the literature up to 1931 on prophylaxis of measles with convalescent serum has been compiled by Thomson and Thomson.[7]

It is difficult to evaluate the results of prophylaxis of measles reported by many investigators because of different methods employed, lack of certain essential

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6. (*a*) Park, W. H., and Freeman, R. G., Jr.: The Prophylactic Use of Measles Convalescent Serum, J. A. M. A. **87**:556 (Aug. 21) 1926. (*b*) Morales, E. G., and Mandry, O. C.: Relative Prophylactic Value of Convalescent and Immune Adult Measles Serum, Am. J. Dis. Child. **39**:1214 (June) 1930. (*c*) Levinson, S. O.; McDougall, C., and Thalhimer, W.: Value of Convalescent Serum for the Prevention and Attenuation of Measles, Illinois M. J. **63**:258, 1933. (*d*) Bundesen, H. N.; Fishbein, W. I.; Abrams, I. R., and Miller, R. D.: Clinical Use of Immune Human Placental Globulin in Chicago, J. A. M. A. **115**:104 (July 13) 1940. (*e*) Top, F. H., and Badger, G. F.: Measles in Detroit, 1935: The Protective Use of Measles Convalescent Serum, Am. J. Hyg. **33**:9, 1941.

7. Thomson, D., and Thomson, R.: The Role of the Streptococci in Measles, Ann. Pickett-Thomson Research Lab. **7**:333, 1931.

information about groups observed and absence of suitable controls. Thus, it has been shown by Karelitz [8] that a higher rate of protection is obtained in contacts exposed to measles in hospitals, schools and homes with good hygienic conditions than in those exposed in crowded homes in which sanitary conditions are poor. Moreover, reports from doctors in private practice also have shown a higher rate of protection. Part of this is probably real, because families of their patients live in homes in which hygienic conditions are good and in which contacts can be isolated early and adequately, and part is only apparent, because in some instances too much reliance has been placed on the observations of parents. Results have been listed only infrequently according to the age of contacts to whom injections have been given. Most of the emphasis has been placed on the interval between the exposure and the injection, but often no mention has been made as to whether the first day of exposure for the contact was counted from the onset of the illness or from the appearance of the rash in the primary source patient. Tabulations have not always differentiated between complete and partial protection. This information is necessary to interpret a report properly.

The purpose of our work, begun in 1938, was to investigate further the measles-protective properties of convalescent serum and the factors that influence the results of its use. The chief factors considered here are age of contact, dosage of serum, interval between exposure and injection and duration and intimacy of exposure. We have standardized each of these factors individually as much as possible. Since a certain proportion of susceptible persons, varying with age, normally escape infection, allowance has been made for this on the basis of a control study of contacts who have not received injections in families of patients with measles. It is recognized that prophylactic results are influenced by other factors, such as host resistance, the severity of the prevalent measles and possibly the virulence of the virus. For example, the severity of measles, as judged by the mortality rate, has made a dramatic decline during the past twenty years. The case fatality rate in 1921 was 2.1 per cent, while during 1938 and 1941 it ranged from 0.1 to 0.03 per cent.[9] These factors affect the comparability of different studies but not the validity of a controlled study of the type presented here.

SOURCE OF MATERIAL AND METHOD OF STUDY

This investigation was conducted in New York city from 1938 to 1941. Since it has been shown that the incidence and the fatality rates are highest in crowded homes with poor hygienic conditions,[10] the work was carried out in congested tenement districts. Only susceptible children exposed to a family member having measles were considered suitable as contacts in the series [11] of patients to whom serum was given and in the control series.[12] Information concerning susceptible

8. Karelitz, S., and Karelitz, R. F.: The Significance of the Condition of Exposure in the Study of Measles Prophylaxis, J. Pediat. **13**:195, 1938.

9. Vital Statistics, in Annual Reports of the Department of Health of the City of New York, 1921-1941.

10. (*a*) Picken, R. M. F.: Epidemiology of Measles in a Rural and Residential Area, Proc. Roy. Soc. Med. (Sect. Epidemiol.) **14**:75, 1921. (*b*) Chalmers, A. K.: The House as a Contributory Factor in the Death Rate, ibid. **6**:155, 1913. (*c*) Debré and Joannon.[3]

11. Stillerman, M., and Thalhimer, W.: Attack Rate and Incubation Period of Measles, Am. J. Dis. Child., this issue, p. 15.

12. In 1941 an outbreak of German measles was prevalent in New York city. To minimize possible errors in diagnosis during this outbreak, contacts were considered for injection only when Koplik spots were observed in the primary patient, and contacts were observed as controls only when the primary patient was seen in the acute stage of measles.

children was obtained from the records of patients with measles at the Willard Parker and the Kingston Avenue Hospital, and when the patients remained at home notification of contacts was received from the Department of Health, the Henry Street Visiting Nurse Service and the children's clinics of the Bellevue and the New York Hospital. All the contacts were healthy children. Those with a questionable history of previous measles were eliminated. Likewise, no contacts were included who had been exposed to measles in hospitals, schools or nurseries or anywhere outside of their own homes, because of the uncertainty and the differences of exposure.

TABLE 1.—*Age Distribution of 502 Subceptible Family Contacts Given Injections of Measles Convalescent Serum (1938 to 1941) and of 245 Susceptible Controls Not Given Injections (1940-1941)*

Age	Number		Per Cent	
	Contacts Given Injections	Controls	Contacts Given Injections	Controls
6-11 months	52	30	10.4	12.2
1 year	90	43	17.9	17.6
2 years	69	26	13.7	10.6
3 years	78	33	15.5	13.5
4 years	58	30	11.5	12.2
5 years	54	24	10.8	9.8
6 years	22	21	4.4	8.6
7 years	27	9	5.4	3.7
8 years	19	9	3.8	3.7
9 years	16	7	3.2	2.9
10 years	6	6	1.2	2.4
11 years	4	1	0.8	0.4
12 years	2	2	0.4	0.8
13 years	0	2	0	0.8
14 years	3	1	0.6	0.4
15 years	2	1	0.4	0.4
Total	502	245	100.0	100.0

TABLE 2.—*Day of Exposure 502 Contacts Received Injections of Convalescent Measles Serum*

Day	Number	Per Cent
2	1	
3	12	2.4
4	71	14.2
5	159	31.7
6	144	28.7
7	90	18.0
8	25	5.0
Total	502	100.0

The convalescent serum used in this investigation was prepared by pooling serum obtained from the blood of thirty or more adolescents and adults with negative Wassermann reactions at intervals up to four months after the onset of measles.[13] The average period after the onset of the disease before the pooled serum was collected from the donors was sixty days.

There were 502 susceptible contacts who were given convalescent measles serum. Their ages ranged from 6 months to 15 years (table 1). Prophylactic injections were administered up to the eighth day after exposure. The beginning of the exposure was estimated by considering the day the rash appeared in the patient as the fourth day of exposure of the contact. The day of exposure on which the contacts received injections appears in table 2. To provide the severest

13. Thalhimer, W.: The Value of Convalescent Scarlet Fever, Measles and Mumps Serums in Prophylaxis and Therapy, M. Clin. North America **23**:613, 1939.

test possible for the serums in 1940-1941, the parents were encouraged to place the contact who had received an injection in the same room with the patient. Follow-up examinations were made by one of us (M. S.) every day or every other day from the ninth to the twenty-third day of exposure, unless the disease occurred during the interval. If symptoms developed, the contact was examined daily until the symptoms subsided. Routinely, on all visits, the contact was stripped, and the following data were recorded: general health, symptoms, rectal temperature and condition of the skin, eyes, nose, mouth, pharynx and glands. Other parts of the body were examined when need was indicated.

A control series of 245 children of the same ages and from the same sources as the contacts receiving injections was gathered during the New York city epidemic of 1940-1941 (table 1).[11] Only those contacts were included who were exposed to a patient seen when the attack of measles was in the acute stage. No attempt was made to encourage a closer than normal association between contacts and patients, as was done with contacts to whom injections had been given. The contacts were followed for evidence of measles from nine to twenty-three days after exposure, or, if the disease developed, until the rash appeared. The proportion of controls not having measles after the first exposure is shown for successive

TABLE 3.—*Children Not Contracting Measles Among 245 Susceptible Contacts Not Receiving Injections on First Exposure to Patients with Measles in 1940-1941*

Age	Total Number of Contacts	Not Having Measles	
		Number	Per Cent
6-11 months	30	11	37
1 year	43	6	14
2-3 years	59	6	10
4-5 years	54	7	13
6-7 years	30	4	13
8-9 years	16	5	31
10-15 years	13	11	85

age periods in table 3. A third of the contacts between 6 months and 1 year of age did not contract the disease. The proportion of children immune to the disease dropped sharply and was at a more or less constant low level, of 10 to 14 per cent, for those between the ages of 1 and 7 years. For children past the age of 7 years the rate climbed rapidly again.

Ordinarily protection from or modification of measles is sought according to the age and the health of the contact. Complete protection is indicated for all susceptible children under 2 years of age, because measles is most serious during this age period, and for those acutely or chronically ill. Modified measles usually is desired for all other children, because the disease is mild, is rarely associated with complications and confers a strong, probably lifelong immunity.

CLASSIFICATION OF MODIFIED MEASLES

In evaluating the dosage of serum, we were primarily interested in obtaining complete protection. However, modified measles developed frequently in contacts receiving serum either in insufficient quantity or late in the incubation period. The degree of modification of the measles of these children was recorded according to a classification based on three cardinal symptoms and signs of regular measles, namely, catarrhal symptoms, fever and rash. Under catarrhal symptoms we considered the redness of the mucous membrane of the eyes, nose and throat, the type of nasal secretion and the frequency of the cough. In rating fever we took into

account the height and the duration of the temperature. The rating for the rash was estimated roughly by recording the number, the intensity and the distribution of the lesions. Each of the cardinal symptoms or signs was subdivided according to degree into A, B and C, the A symptoms being mild, the B moderate and the C approximating those of full-blown measles of average severity, as follows:

I. Catarrhal Symptoms

Conjunctiva	Nose	Mouth and Pharynx	Trachea and Bronchi
A. Mild redness	Mild redness	Mild redness	Occasional cough
B. Moderate redness	Mucoid discharge	Moderate redness	Moderately frequent cough
C. Marked redness	Mucopurulent discharge	Marked redness	Frequent cough

II. Fever

Height	Duration
A. 100 to 100.9 F.	1 to 2 days
B. 101 to 102.5 F.	3 to 4 days
C. 102.6 F. and over	5 days and longer

III. Rash

A. Few, faint lesions, limited to one third of body
B. Moderate number, red, limited to half of body
C. Many, purple and generalized

The three cardinal symptoms or signs were recorded in terms of combinations of A, B and C. If A, B and C were counted as 1, 2 and 3, respectively, the attack of modified measles was classified as A when the combined total of the three cardinal symptoms was 4 or less, as B when it was 5 or 6 and as C when it was 7 or 8. In regular measles, CCC, the combined total was 9. Various combinations of these symptoms were observed in the contacts receiving injections, such as catarrh and fever without a rash, fever and rash without catarrh, or any one of the signs alone. All three cardinal symptoms, however, should be present definitely if the illness is to be considered modified measles, with the exception of the rash, which alone may be a sign of the disease. The degree of modification necessary to produce a lifelong immunity has not been definitely established.

DOSAGE

The dose of serum required to prevent a potentially mild attack of measles would probably only modify a potentially severe one. Since there is no way of predicting which attacks of measles will be severe, the dosages fixed for severe ones have been used. The dose employed at the beginning of this work in 1938 was 5 cc. for children from 6 months to 5 years and 1 cc. in addition for each year over that age. At that time, this dosage was expected to give protection when the serum was injected on or before the fifth day after exposure but only modification if it was administered from the sixth to the eighth day. If a dose twice as large was used during the latter period, protection was expected. From 1938 to 1941 we tried to determine how much it was possible to increase the rate of complete protection by increasing the dose of serum. Accordingly, the dose was gradually raised to 10 cc. for contacts 6 to 11 months of age, 15 cc. for those 12 to 23 months and 20 cc. for all those 2 years and over. A small number of children 5 years of age were given injections of 30 cc. of serum. Further, in order to determine the effect of age on the results, even though the dose of serum was increased, the amount was fixed for all those of 1 year of age and over at 10 cc. in 1939 and 12 cc. in 1940 and for those of 2 years of age and over at 20 cc. in 1941. For reasons to be noted later, in 1941 only those contacts received injections who were 6 months to 9 years of age and had been exposed not more than seven days. The various plans of dosage used between 1938 and 1941 are given in table 4.

The entire dose was injected intramuscularly into the upper, outer aspect of the buttock or the thigh. There were no reactions other than local discomfort. A preliminary test for cutaneous sensitivity as recommended by Davison [14] was not given, because we have found it unnecessary when properly prepared human serum is injected intramuscularly.

GENERAL RESULTS

The rate of protection against measles and the degree of modification of the measles of the 502 contacts who were given injections of convalescent measles serum from 1938 to 1941 are shown in table 5. Complete protection was obtained by 50 per cent of the contacts, while modified measles occurred in 49 per cent and unmodified measles in 1 per cent. Thus, complete and partial protection was secured by 99 per cent of the contacts to whom injections had been given. Furthermore,

TABLE 4.—*General Plan of Dosage with Convalescent Measles Serum According to Age in Each Year from 1938 to 1941 Inclusive*

Year	6-11 Months	12-23 Months	2-5 Years	6-9 Years	10-15 Years
1938	5 cc.			1 cc. per year of age	
1939	5 cc.		10 cc.		
1940	6 cc.		12 cc.		
1941	8-10 cc.	15 cc.	20 cc.		None given injections

TABLE 5.—*Degree of Modification of Measles in 502 Contacts Receiving Injections of Convalescent Measles Serum from 1938 to 1941*

Degree of Modification	Number	Per Cent
Complete protection	250	50
Other degree of modification, total	248	49
Marked (A)	136	27
Moderate (B)	92	18
Slight (C)	20	4
None (unmodified measles)	4	1
Total	502	100

the degree of modification of the disease was considerable (A) for 27 per cent of the entire series of contacts, or slightly over half those in whom modified measles was obtained. In such attacks the cardinal symptoms are mild, and unless the physician is familiar with them and examines the contacts carefully and frequently, they can be overlooked easily. Failure to recognize many appreciably modified (A) attacks of measles may account in part for the higher percentage of complete protection reported by many physicians in private practice and in other studies. It is significant that our total number of children completely protected or having considerably modified measles combined was 77 per cent, which figure approximates the percentage of those afforded complete protection reported by some investigators. (It is believed that the reason that some observers have reported this high percentage of complete protection is either that they were not able to carry out as careful a follow-up as we did and failed to observe some mild, modified attacks or that the exposures in hospitals, institutions or better class homes were more uncertain and less intimate than those of the children we studied.) More-

14. Davison, W. C.: Reduction of Communicable Diseases Among Troops and Children During National Defense Program, War Med. **1**:863 (Nov.) 1941.

over, it is important to note that most of the remaining attacks of measles were appreciably modified, and in only 4 per cent was the modification of slight degree (C).

RESULTS ACCORDING TO INTERVAL BETWEEN EXPOSURE AND INJECTION

In table 6, according to the day after the exposure the contact received serum, the percentage of protection is shown separately for those receiving doses of 5, 10, 12 and 20 cc. and for those receiving all other doses. From this table it is apparent that there was no significant difference in the rate of protection obtained for contacts of any dosage group given injections from four to seven days after exposure; e. g., whether a child received 5 cc. on the fourth or the seventh day made no significant change in the protection results. On the eighth day, however, the rate of protection decreased sharply, and only 16 per cent of those receiving injections were protected, although modified measles occurred in the remainder. Thus, contrary to the opinion prevalent at the outset of this study, the rate of protection was the same in patients given injections on the sixth or seventh day

TABLE 6.—*Comparison of Rate of Protection According to the Day After Exposure Contacts Received Injections*

	Per Cent with No Disease					Number of Contacts				
Day	All Doses *	5 Cc.	10 Cc.	12 Cc.	20 Cc.	All Doses *	5 Cc.	10 Cc.	12 Cc.	20 Cc.
2	†	†	..	..	..	1	1	..	..	..
3	50	†	†	†	..	12	2	5	2	..
4	46	36	36	58	53	71	14	14	19	19
5	48	27	54	50	56	159	37	37	36	25
6	56	33	54	60	73	144	27	24	53	15
7	56	31	58	57	†	90	13	24	30	5
8	16	†	14	0	..	25	5	7	9	..

* Contacts receiving injections of serum in this column include those given injections of other doses than those listed.

† Percentages for dosage groups of 5 patients or less were omitted.

(modification previously expected) as in those given injections on the fourth to the fifth day after expsoure (protection previously expected).

Furthermore, a similar analysis of the cases of modified measles likewise demonstrated no constant or significant difference in the proportion of A, B and C attacks between the fourth and the eighth day after exposure.

PROPHYLAXIS RESULTS ACCORDING TO DURATION OF EXPOSURE

Since there was no significant difference in the percentage of protection obtained by contacts who had received injections four to seven days after exposure, analysis of the results according to the number of days these children were in actual contact with the patient was thought to be of interest. All contacts who had received injections of serum up to the seventh day after exposure in 1940 and 1941 were studied. When the patient was sent to the hospital the first day the rash appeared, the contact was considered exposed for a period of four days; when he was sent the second day, the contact was thought to be exposed for five days, and when the patient remained at home throughout the illness, the period of contact arbitrarily was considered eight days. It is evident in table 7 that once the rash appeared there was no significant difference in the proportion of protection obtained by children who received injections, regardless of the length of contact. Thus, in these intimately exposed contacts infection occurred before the rash appeared in the patient,

and early separation from the patient of the contact receiving serum did not give rise to a higher rate of protection than that which was recorded for the contacts of those patients who remained at home throughout the entire illness. In other words, unless complications arise, children with measles can be left at home if the contact is given injections.

TABLE 7.—*Comparison of Rate of Protection According to the Number of Days Children Receiving Injections of Serum Were in Actual Contact with the Patient with Measles*

Days of Contact	Number of Cases	Protection or No Disease	Per Cent
3	4	2	*
4	59	30	51
5	38	24	63
6-7	3	1	*
8	171	97	57

* Not given because of small size of group.

TABLE 8.—*Degree of Modification of Measles with Specified Doses* Among Susceptible Contacts Given Measles Convalescent Serum, by Age*

Age: Dosage	Number Given Injections	Complete Protection		Net Protected Per Cent †	Modification			Unmodified (Measles)
		Number	Per Cent		Marked (A)	Moderate (B)	Slight (C)	
6-11 months								
5 cc.	15	10	67	30	3	2	..	..
6 cc.	19	11	58	21	4	4	..	..
8 cc.	8	4	50	13	3	1	..	..
10 cc.	7	7	100	63	..	..	..	..
1 year								
5 cc.	28	9	32	18	12	6	1	..
10 cc.	19	8	42	28	7	4	..	..
12 cc.	19	17	89	75	2	..	..	..
15 cc.	16	14	88	74	2	..	..	..
2-3 years								
5 cc.	29	5	17	7	10	10	3	1
10 cc.	42	25	60	50	12	5	..	..
12 cc.	43	27	63	53	12	4	..	..
20 cc.	24	19	79	69	4	1	..	..
4-5 years								
5 cc.	20	5	25	12	8	4	3	..
10 cc.	27	11	41	28	8	8	..	..
12 cc.	29	8	28‡	15	11	9	1	..
20 cc.	23	12	52	39	7	4	..	..
30 cc. §	6	3	50	37	3	..	..	..
6-7 years								
6-7 cc.	8	2	25	12	..	4	2	..
10-12 cc.	31	16	52	39	8	3	5	1
20 cc.	9	4	44	31	1	3	1	..
8-9 years								
10-12 cc.	18	10	56	25	3	5	..	..
20 cc.	9	3	33	2	2	3	..	1
10-15 years								
10 cc.	6	4	67	..	..	1	1	..
12 cc.	8	5	63	..	1	1	..	1

* Excludes contacts given injections on eighth day of exposure and dosage groups of 5 children or less given injections at the specified ages.

† Per cent protected in preceding column minus per cent immune at corresponding age among controls not given injections (table 3).

‡ At 4 years of age, 7 of 14 children (50 per cent) were protected, but at 5 years of age only 1 of 15 (7 per cent).

§ Children at 5 years of age only in 1941.

EFFECTS OF AGE AND DOSAGE ON THE RESULTS

In table 8 are presented the results obtained according to the dosages used for children at specified ages under 2 years and at certain combinations of ages up to 15 years. The table presents the number of patients completely or partly protected, as already described, but the percentages have been computed only for those children who were completely protected. Since some allowance must be made for natural

or acquired immunity, a column showing what may be termed a net ratio of protection has been added. This was arrived at by deducting from the gross rate of protection the proportions of contacts at corresponding ages who had not received injections and who did not acquire measles in the control series referred to in table 3. These net figures must not be taken as absolute, first, because the samples of children at various ages who constitute the series of those receiving injections and the control series are usually sufficiently small to make the net figures have a comparatively large error due to chance variation, and, second, because this involves the reasonable assumption that the group receiving injections have the same degree of immunity as the controls.

The gross figures of complete protection are considered first. When the effect of age on the results of measles in the contacts given serum was studied at the end of the 1938 season, there seemed to be indications of a relatively greater benefit to extremely young children. Thus, of children 6 to 11 months of age, 67 per cent were protected with 5 cc. doses, but only 32 per cent at 1 year of age and even smaller percentages of those older. It was, however, somewhat difficult to evaluate results in those over 5 years of age because a dosage ascending in scale with age was employed. Moreover, the samples of children over 5 years of age were small in 1938.

When, as already described, doses higher than those given in 1938 were used, it was found generally that for children up to 4 years of age the increase of doses, up to 10 cc. for infants, 15 cc. for children 1 year of age and 20 cc. for those 2 and 3 years of age, gave better results, although not every increase in dose was attended with an improved degree of protection. Thus, of the small number of infants given 10 cc. of serum the routine use of this dose gave complete protection to all, but nothing like this result had been achieved with doses from 5 to 8 cc. In the second year of life a slight but not significant increase in the proportion of children protected was obtained by increasing the dose from 5 to 10 cc., but a much greater increase in the number protected against measles was obtained when the dose was further increased to 12 cc. Approximately the same result was obtained with 12 as with 15 cc. of serum at this age.

For children between 2 and 3 years of age a substantial increase was obtained in the proportion protected when the dose was increased from 5 to 10 cc. of serum. Further increase to 12 cc. did not bring significant improvement in the results, but there was a further considerable rise with a dose of 20 cc.

For children 4 and 5 years of age there was a substantial improvement in the results with 10 cc. of serum as compared with 5 cc., but no appreciable improvement with doses of 12, 20 and not even with 30 cc. in a small group of experimental children 5 years of age. On the whole, in children over 5 years of age the comparative results with doses of 10, 12 and 20 cc. were substantially the same. The gross figures at these ages, particularly for those 10 years or older, were sometimes higher than for the younger children. Either or all of several factors may have been responsible for this result, namely, the small number and therefore the statistical unreliability of the sample of older children observed, their natural or acquired immunity or the differences in their mode of life.

The net rate of protection recorded in the fourth column of table 8 shows a definite downward trend as one reviews the figures from the youngest to the oldest age groups. The degree of modification also tends to become less pronounced with increasing age of the contacts. This would indicate that progressively larger prophylactic doses are necessary for children of increasing age to maintain a constant high level of protection.

A review of both the gross and the net figures of protection as well as those of modification indicates that the following routine practices are advisable in the use of convalescent measles serums. If complete protection is desired for infants under 1 year, a minimum dose of 10 cc. of serum is probably required. For infants 1 year of age 12 cc. appears to be the minimum dose necessary, and although 15 cc. gave no better results, it may be a conservative policy to increase the dose to that figure. For children 2 and 3 years of age 20 cc. appears advisable, although as little as 10 or 12 cc. has given complete protection to a bare majority of nonimmune children 2 and 3 years of age in this series (net figure). For children 4 years of age or more the highest rate of protection was generally obtained when the dose was increased to 20 cc., but this dose did not give protection to a majority of the nonimmune children (net figure). The results generally seem to indicate that it is not worth while, except for children with complications, to strive for complete protection of those 4 years of age and over, and even if the attempt is made, one may not count on obtaining more than a considerable modification of the disease. This applies particularly to persons from 10 to 15 years of age, for the reasons cited earlier.

Since complete protection is not always attainable or desirable for measles contacts, consideration may also be given to the doses that will greatly alleviate the oncoming illness and also protect the patient from subsequent attacks. Examination of table 8 indicates that for this purpose 5 cc. of serum is sufficient for children up to 24 months of age and 10 cc. for older children.

DURATION OF PASSIVE IMMUNITY IN COMPLETELY PROTECTED CONTACTS

During 1941 we followed 13 children 17 months to 5 years of age in families of 3 or more children in which the contact receiving an injection did not have measles and was subsequently reexposed to a member of the family who did have the disease. In 11 instances the reexposure was to regular measles and in 2 instances to modified measles. The reexposures occurred seven to thirty-six days after the injection. Of 11 contacts exposed seven to fourteen days after the injection not one had measles, while 2 exposed twenty-five and thirty-six days after the injection had unmodified measles.

CHARACTERISTICS OF MODIFIED MEASLES

The modified measles manifested bizarre and varied forms. The appreciably modified attacks were extremely mild, and the children were not sick, while the slightly modified C attacks approximated but were less severe than those of regular measles. The involvement of the eyes, nose, throat and bronchi was not always uniform, infection in one of these often predominating. For instance, in some mild attacks there was no cough. The oral lesions might show redness of varying degree and petechiae or aphthous areas on the palate and the buccal mucosa. When the tonsils were intact, white follicles were often present on a normal or slightly reddened mucosa, whereas in regular measles the follicles, when present, were found on a more reddened mucosa. These follicles were noted before, during and after the appearance of Koplik spots on the buccal mucosa. The Koplik spots were usually absent in the A and the B attacks and were altered in the C attacks. The height and the duration of the temperature varied considerably. In some cases the fever was low and lasted five to six days or was high and lasted one to two days. Adenopathy was present but was not severe. The rash when mild

usually was seen only on the trunk—particularly on the back. Next in order of its appearance were the face and the proximal portions of the extremities. The mild rash consisted of discrete scattered pink papules with no macular element and varying in diameter from 2 to 4 mm. When the rash was more intense a macular element was present. The B rash might consist of scattered discrete generalized lesions or a fair number of closely set ones on the trunk and a few on the face. The rash when mild lasted one to two days, while the more intense rashes persisted for a longer time and sometimes were followed by a yellow spotty staining. Desquamation was uncommon.

In a comparison of the degree of modification of each of the three cardinal symptoms with that of the illness as expressed in the previous classification, it was found that the catarrhal symptoms were modified and were helped most and the fever least, while the rash coincided most closely with and in the average case was the best indicator of the degree of modification. The general well-being of

TABLE 9.—*Comparison of the Number of Days from the Onset of Rash in Original Patients with Measles with That in Contacts Given Injections and the Controls Not Given Injections Having Modified Measles or Regular Measles After First Exposure*

Days Between Onset of Rash in Original Patient and in Contact	Number		Per Cent	
	Contacts Given Injections	Controls	Contacts Given Injections	Controls
7	3	..	1.2	...
8	4	3	1.7	1.5
9	20	9	8.3	4.6
10	24	27	9.9	13.8
11	39	28	16.1	14.4
12	41	43	16.9	22.1
13	46	28	19.0	14.4
14	26	30	10.7	15.4
15	15	12	6.2	6.2
16	12	5	5.0	2.6
17	6	7	2.5	3.6
18	4	2	1.7	1.0
19	1	1	0.4	0.5
20	..	..	...	...
21	1	..	0.4	...
Total	242	195	100.0	100.0

the contact who had received an injection, however, was associated more closely with the degree of the catarrh, and particularly of the cough, than with the fever or the rash.

Analysis was made of the number of days between the appearance of the rash in the patients with the primary attack of measles and its appearance in the contacts given injections and the controls not receiving serum who had modified or regular measles after the first exposure. This is not the true incubation period, which by definition is the interval between the time of infection and the onset of symptoms. The appearance of the rash rather than the onset of symptoms was selected as the starting point, first, because in homes it could be determined more accurately and secondly because it was not known when the contact was infected, even though the first day of exposure was known. Comparison of the intervals of the two groups is given in table 9. The source of the material was the same and the age distribution similar (table 1). The interval in days between the primary and the secondary attack of measles has been tabulated by age for the control series.[11] Computation showed that the interval of ten to fourteen days

was most frequent for both groups. There was a slight tendency toward a higher proportion of intervals of fifteen days or more for the contacts receiving injections, but in no case was the difference significant. On statistical grounds, therefore, it is justifiable to conclude from the foregoing data that the "incubation period" of the group given serum who had modified measles was not prolonged.

COMPLICATIONS IN MODIFIED MEASLES

In the entire series of patients who had received serum there were few complications. These consisted of conjunctivitis in 1 patient, catarrhal otitis media in 3 patients and purulent otitis media in 2 patients. One of the latter conditions was a flare-up of chronic otitis media. There were no deaths.

COMMENT

The impression has apparently developed from the work of previous investigators that if enough convalescent serum is administered to a child soon after exposure to measles the disease will always be prevented. It is well established from experience that 100 per cent protection under optimum conditions does not occur and cannot be expected. There is no immunizing or prophylactic agent known in the entire field of infectious diseases which has this complete degree of reliability. Many studies of the prophylactic efficiency of measles convalescent serum have indicated that it has from 70 to 90 per cent efficiency. The groups reported have often included exposures of children in hospitals, schools and nurseries, at play or in better class homes as observed in private practice. Exposures of this type are well known to be of irregular occurrence and of varying degrees. Sometimes all the patients of a hospital ward thought to be exposed to measles escape infection, and at other times an apparently similar exposure will result in development of the disease in almost the entire susceptible ward population. In private practice contacts are often isolated early in homes with good hygienic conditions, and the physician is rarely called to observe the child to whom serum had been given day by day during the end of the incubation period. In fact, even if the child has mild modified measles, the physician may not be notified, because the child's parents may not notice the condition or may attribute it to some other cause, such as teething, food, heat or a cold. The child may be tabulated as protected when the disease is merely modified.

In this study, contacts were considered as suitable subjects for treatment by injection or for use as controls only when there was a prolonged intimate exposure with a primary patient with measles in the same family living in a crowded home, and after the history of a possible previous attack of measles in the contact was excluded. All observations were made by one of us daily or every other day from nine to twenty-three days after the onset of the exposure or until the development of the disease, and it is unlikely that any attack of measles or modified measles was missed.

SUMMARY AND CONCLUSIONS

From 1938 to 1941 a group of 502 intimately exposed susceptible family contacts from 6 months to 15 years of age were given injections of convalescent measles serum. Certain factors that influenced the results of prophylaxis of measles for these 502 children were studied, as well as the proportion of natural or acquired immunity in a control group of 245 subjects of similar ages who had not received injections observed in 1940-1941.

For the control group of children the rate of immunity varied with age. Of children 6 months to 11 months of age one third did not have measles on first exposure; of those between 1 and 7 years 10 to 14 per cent escaped the disease; of those from 8 to 9 years of age 31 per cent were immune, and of the small group between 10 and 15 years of age 85 per cent were immune.

The dose according to age was raised yearly during 1938 to 1941 from a minimum in 1938 of 5 cc. for those up to 5 years of age, with 1 cc. for each additional year, to a maximum in 1941 of 10 cc. for those 6 to 11 months, 15 cc. for those 12 to 23 months and 20 cc. for those 2 years of age and over. A small number of children 5 years of age received 30 cc.

Complete protection was obtained by 50 per cent of the 502 children. Modified measles occurred in 49 per cent and unmodified measles in 1 per cent of these 502 patients. The modification was appreciable in 27 per cent of the entire group, or slightly over half of those with modified measles, moderate in 18 and slight in 4 per cent. Thus, in 95 to 99 per cent of the 502 children receiving injections measles either did not develop or was definitely modified.

The rate of complete protection, analyzed according to the interval between the exposure and the injection, showed no significant difference between the fourth and the seventh day after exposure in those groups receiving separately doses of 5, 10, 12 and 20 cc. and for all dosage groups combined. However, on the eighth day after exposure, even though the serum had a definite modifying effect, it did not prevent measles.

Comparison between the rates of protection obtained in contacts who had received injections when the patient with measles was removed to a hospital on the first or second day after the rash appeared and when the patient remained at home throughout the illness showed no significant difference.

The duration of passive immunity of contacts completely protected with doses of 20 cc. of serum was found to be at least two weeks.

For the group that had received serum a classification of modified measles was devised according to the degree of modification of the three cardinal symptoms and signs of regular measles, namely, the catarrhal symptoms, the fever and the rash. On this basis it was found that in the average case the catarrhal symptoms were helped and modified the most and the fever the least, while the rash coincided closest with and per se was the best indicator of the degree of modification.

The "incubation period," as measured by the interval between the onset of the rash in the patient with measles and that in the contact, was compared for the contacts receiving serum and the controls in whom measles or modified measles developed. There was no statistically significant difference between the two groups.

Mild complications developed in only 5, or 1 per cent, of the 502 contacts who received injections of serum.

In plans for complete protection or modification of measles of susceptible children intimately exposed to measles, the age of the contact and the dose of serum are the two most important measurable factors which influence the result.

Complete protection is recommended for all exposed healthy susceptible children under 2 years of age, because it postpones the attack until they are older, when there is a reduced case fatality rate, and is advised also for contacts over this age who are acutely or chronically ill. Modified measles is indicated for healthy children over 2 years of age, because this condition is a mild disease rarely associated with complications and is followed by strong and lasting immunity.

For complete protection the optimum dose after an exposure of four to seven days is 10 cc. for contacts 6 to 11 months of age, 15 cc. for those 12 to 23 months

and 20 cc. for those 2 and 3 years of age. For healthy contacts 4 years and over, complete protection is not worth striving for, partly because serum in amounts up to 20 cc. cannot be relied on to prevent the occurrence of measles in a majority of nonimmune children and partly because modified measles is more desirable at these ages.

If modified measles is desired, 5 cc. is sufficient between the fourth and the eight day after exposure for contacts up to 24 months of age, and 10 cc. for those older.

Drs. Ralph Muckenfuss, Samuel Frant, Frank Calderone, Sophie Rabinoff, Franklin Foote and their staffs, of the New York City Health Department; Miss Katherine Faville and her staff, of the Henry Street Visiting Nurse Service; the medical boards of the Kingston Avenue and the Willard Parker Hospital, and the pediatric departments of the New York and the Bellevue Hospital cooperated in making this study possible. Dr. Harold Fuerst assisted on the 1938 field study.

Fifteenth Street and East River.

ATTACK RATE AND INCUBATION PERIOD OF MEASLES

SIGNIFICANCE OF AGE AND OF CONDITIONS OF EXPOSURE

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In 1940 and 1941 we had the opportunity to study certain aspects of the attack rate of measles which we believe to be of value in the study of the epidemiology of this disease. That not all supposedly susceptible children will have measles after a particular exposure has been known for many years. Stocks [1] has estimated that for every clinical case of measles in a densely populated area there are three times that number of children who become temporarily immune because of latent infection. It is reported, however, that in urban communities 90 to 95 per cent of persons will have contracted this disease by the time they attain adult life.[2] The purpose of this paper is to record the attack rate and incubation period of measles in the 1940-1941 epidemic in New York city and to analyze certain sginificant factors that may affect the results.

The effect of host resistance has not received much attention in determining the attack rate of susceptible children exposed to measles. This has been largely because of the lack of suitable methods for measuring immunity to this disease. All known secondary attack rates recorded by previous investigators [3] according to individual ages are given in table 1. These figures, except those of Morales and Mandry,[3f] are based on the records of family cases reported to the various health departments.

A large number of susceptible children intimately exposed to measles in families living in crowded tenement homes of New York city were observed as part of a study of prophylaxis of measles with convalescent serum.[4] To analyze properly the prophylactic effect of the convalescent serum, it was necessary to correct for the factor of immunity. This was computed by deducting from the rate of protection

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From the Human Serum Division of the Public Health Research Institute of the City of New York, Inc.

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4. Stillerman, M.; Marks, H. H., and Thalhimer, W.: Prophylaxis of Measles with Convalescent Serum: Principal Factors Influencing the Results, Am. J. Dis. Child., this issue, p. 1.

obtained among children who had received injections of serum the proportion of contacts of corresponding ages who had not received injections and who would not be expected to contract measles during a current epidemic. Such a control group exposed under conditions similar to those in which the contacts who had received injections lived was studied in the 1940-1941 epidemic. Contacts were

TABLE 1.—*Secondary Attack Rate of Measles Among Susceptible Family Contacts, Classified by Age* *

Age in Years	Chapin [2c] Providence 1917-23	Wilson et Al.[2c] Providence 1929-34	Fales [2d] Baltimore 1936-37	Top [2e] Detroit 1935	Butler [2b] Willesden 1908-11	Morales and Mandry [2f] Puerto Rico 1928	Chapin [2c]	Wilson et Al.[2c]	Fales [2d]	Top [2e]	Butler [2b]	Morales and Mandry [2f]
	Per Cent						Number of Contacts					
Under 1	47	41	32	47	47	..	1,208	562	585	165	383	...
1	86	86	77	92	84	..	958	573	593	178	242	...
2	90	89	79	91	89	..	1,084	652	657	246	248	...
3	88	89	84	93	90	..	1,115	716	654	304	323	...
4	89	90	84	91	83	..	1,055	766	729	255	316	...
5	88	90	81	87	72	..	781	670	582	207	172	...
6	85	89	86	83	65	..	497	439	389	107	103	...
7	85	87	81	80	52	..	342	332	256	75	125	...
8	77	84	80	79	44	..	318	279	199	56	88	...
9	72	74	68	60	43	..	187	214	144	40	68	...
10	57	75	54	..	..	..	157	131	112	...	...	...
11	48	62	52	..	..	..	95	104	85	...	...	...
12	39	51	43	..	18	..	62	53	53	...	201	...
13	36	30	26	..	..	..	53	33	58	...	...	...
14	27	27	22	..	..	..	33	30	31	...	...	...
Total	79	80	73	85	67	81	7,945	5,554	5,107	1,633	2,369	183
1-4	88	88	81	92	87	93†	4,212	2,707	2,633	983	1,129	96
5-9	84	86	81	82	58	78	2,125	1,934	1,550	485	556	66
10-14	47	59	44	..	18	43	400	351	339	...	201	21

* Institutional and nonresident patients not included.
† Contacts 6 months to 4 years inclusive.

TABLE 2.—*Attack Rate of Measles Among 266 Exposed Susceptible Family Contacts in New York City, 1940-1941*

Age in Years	Total Number of Contacts	Incidence of Measles	
		Number	Per Cent
Under 1	51	23	45.1
1	43	37	86.0
2	26	24	92.3
3	33	29	87.9
4	30	25	83.3
5	24	22	91.7
6	21	18	85.7
7	9	8	88.8
8	9	6	66.6
9	7	5	71.4
10-14	13	2	15.4
Total	266	199	74.8
1- 4	132	115	87.3
5- 9	70	59	84.3
10-14	13	2	15.4

considered suitable controls only when the patient who was the source of the infection (primary case) was seen when the measles was in the acute stage. Children with a questionable history of a previous attack of measles were excluded. Children exposed in hospitals or nurseries, at play or anywhere other than in their own homes were not included, because of the uncertainty and the variant degrees of exposure. The control contacts were followed from nine to twenty-

three days after the beginning of the exposure unless the rash developed before that.

The incidence of measles in this epidemic was the highest ever reported in New York city. The outbreak began in November of 1940 and pursued its course for eight months, with its peak in April 1941. The cases in this report were gathered during this entire season.

The secondary attack rate among 266 contacts who were exposed to a family member with measles is given for successive ages from 0 to 9 years and for the age group 10 to 14 years in table 2. The attack rate rose abruptly from only 45 per cent for those under 1 year to 86 per cent for those at the age of 1 year and changed little from this figure for children up to the age of 7 years. For children between 8 and 9 years of age the rate declined to an average of 69 per cent and for the oldest group it dropped sharply to 15 per cent. For all ages combined the rate was 75 per cent.

The incidence of measles among 51 exposed infants under 1 year of age is recorded by months in table 3. Measles did not occur in 10 contacts less than

TABLE 3.—*Incidence of Secondary Measles in Infants Under 1 Year of Age*

Age in Months	Total Number	Number with Secondary Measles	Per Cent
1	3	0	
2	2	0	
3	5	0	
4	7	1	
5-8	22	12	55
5	4	3	
6	7	3	
7	4	2	
8	7	4	
9-11	12	10	83
9	5	3	
10	4	4	
11	3	3	

4 months of age and occurred in only 1 of 7 contacts 4 months of age. Subsequently the attack rate rose sharply, and for infants 9 to 11 months of age the rate was about the same as that for children 1 year of age.

There were 21 susceptible children 6 months to 10 years of age who did not have measles after the first exposure and who were reexposed to a family member who did contract the disease. Of these children, 13 (or 38 per cent) contracted measles. This attack rate is about one half of that (75 per cent) of the susceptible contacts exposed a first time.

The effect of duration of exposure on the attack rate was also investigated. This was based on experience with 56 contacts who were separated from the source of the infection early. These children, 6 months to 9 years of age, were exposed to 36 patients with measles who had been hospitalized, 21 on the day the rash appeared and 11 the day after the rash appeared. Measles developed in 44 (or 79 per cent) of the 56 contacts. This rate corresponds to that of 74 per cent recorded for the 210 children who were exposed at home throughout the illness of the patients. Infection in these intimately exposed contacts occurred before the onset of the rash in the patient, and once the rash had appeared, early separation of the contact from the patient did not alter the secondary attack rate.

The effect of increased intensity of exposure, as measured by the attack rate among susceptible contacts exposed simultaneously to 2 patients with measles in the same family, appeared to be of little significance. Of the 9 contacts with

multiple exposures, measles occurred in 7 (or 78 per cent). This proportion is about the same as that for all other contacts, but the number is too small to permit a definite conclusion.

The interval in days between the occurrence of the first and that of the second case of measles in a family was analyzed according to ages of the patients. The appearance of the rash rather than the onset of the symptoms was taken as the measuring point at home, because first, it could be ascertained more definitely and, secondly, the time of infection could not be determined accurately even though the period of exposure was known. As Stocks [5] has pointed out, for statistical purposes in homes the interval between the onset of the rash in the first and that in the second case of measles is as good a measure of the incubation period as any which can be obtained. The interval between the onset of the rash in the patient and its onset in the contact contracting the disease after the first exposure varied from eight to nineteen days (table 4). In the great majority of cases (80 per cent) it was ten to fourteen days. The period was longer than fourteen days in 28 cases (14 per cent) and less than ten days in 12 cases (6 per cent). There was a tendency for the longer intervals to occur more frequently among the younger contacts, but the proportion of contacts with intervals exceeding fourteen days was significantly higher only for those 12 to 23 months old.

TABLE 4.—*Interval in Days Between Onset of the Measles Rash in the Patient and Its Onset in the Family Contact*

Age of Contact in Years	Number of Days												Total Cases	Average Interval
	8	9	10	11	12	13	14	15	16	17	18	19		
Under 1	..	..	4	2	2	3	6	3	..	3	..	..	23	13.3
1	..	1	4	4	6	6	4	2	3	4	2	1	37	13.5
2	..	..	4	1	7	5	5	1	1	..	..	..	24	12.5
3	..	1	6	5	8	2	5	1	1	..	..	..	29	12.0
4	..	3	3	5	4	3	4	1	..	2	..	..	25	12.2
5	..	..	3	5	9	2	2	1	..	..	..	..	22	11.9
6	1	1	2	3	5	3	2	1	..	..	..	..	18	11.8
7	..	3	1	..	..	2	2	..	..	..	..	..	8	11.4
8	2	..	..	1	2	1	..	..	..	..	..	..	6	10.7
9	..	..	1	2	1	1	..	..	..	..	..	..	5	11.4
10-14	..	..	..	..	..	1	..	1	..	..	..	..	2	14.0
Total, all ages	3	9	28	28	44	29	30	11	5	9	2	1	199	12.4

The fact that younger children appeared to contract measles more slowly than older ones led us to tabulate according to seniority the numbers of days before the onset of the rash in 2 or more susceptible family contacts to whom the disease had been transmitted from the same primary source of infection. Of 33 such families the interval was longer for the younger of the patients with secondary measles in 23, shorter in 5 and the same length in the remaining 5. Irrespective of seniority, the difference in the time elapsing between the secondary attacks from the same source ranged from zero to five days in all but 1 instance. In that instance, it was seven days. Of further interest was the fact that for each of 3 sets of twins similarly exposed the intervals before the onset of the rash also varied, being eleven and fourteen days, fifteen and sixteen days, and twelve and seventeen days, respectively.

COMMENT

The attack rates recorded by other investigators and by ourselves were about the same for contacts up to 10 years of age. In the 10 to 14 year group, however, the rate was much lower both in Butler's cases and in ours. The low rate

5. Stocks, P.: Incubation Period of Measles, Brit. M. J. 1:157, 1931.

in early infancy was due partly to the children's passive immunity acquired from their mothers and in part to the smaller degree of exposure of infants too young to walk. During the second half of the first year the proportion of secondary attacks became greater, as the congenital immunity wore off. The highest attack rate in each recorded series occurred in contacts 1 to 5 years of age. In those over 7 years there was a definite tendency for the rate to decrease as the age increased. This apparent resistance of certain older persons may be due in part to lessened chance of infection because of differences in mode of life or of a definite immunologic mechanism.

An experience encountered by one of us (M. S.) in a private suburban school in April 1941 may help to explain certain differences in the attack rate between city and suburban children in the upper age group. A small class (11) of children 11 to 12 years of age was exposed from 9 a. m. to 9:35 a. m. on Monday to a classmate who was sneezing and coughing. On the following Thursday, this child, who was isolated at home, had a full-blown rash of measles. Of the 11 exposed children, the 6 who had never had measles all contracted the disease from eleven to fourteen days after the thirty-five minute exposure. A similar experience was described by Butler with a much larger group of children, 13 to 17 years of age, in a suburban boarding school in which the attack rate of measles was much higher than that in urban schools among adolescents of similar ages.

The higher incidence of measles among older children in suburban than in urban schools probably reflects the fewer opportunities of young children in communities with low density of population to become infected. Consequently the decrease in attack rate that occurs with increase in age over 7 years among urban children is due not to factors inherent in growth per se but rather to the opportunity city life provides for acquiring an active immunity through repeated exposures to minor or attenuated doses of infection. This does not, however, explain the variations in the attack rate of measles among the older children listed in tables 1 and 2, in which all recorded cases are presumably from urban centers.

About one fourth of the supposedly susceptible children did not have measles after one intimate exposure. Some of these less susceptible children may not have contracted the disease because of some degree of latent immunity. Of those who escaped infection on the initial exposure and were reexposed, about one half succumbed to the disease. Thus, even though the likelihood of contracting measles on reexposure is less, it nevertheless exists.

The period of exposure necessary to obtain the highest secondary attack rate has not been definitely determined. Karelitz [6] found the ability to prevent measles diminished as the period of exposure progressively increased from the indeterminate or mild exposures that occur in hospitals, schools and nurseries for a few minutes to six hours to the intense and prolonged types present in unhygienic homes for four to eight days. In our study, limited to intimately exposed contacts, we found that by the time the rash had appeared in the patient, i. e., the fourth day of exposure for the family contact, the secondary attack rate was not affected by separation of the patient and the contact. Likewise for a large series of similarly exposed susceptible children who received prophylactic injections of convalescent measles serum between the fourth and the seventh day after exposure, the rate of protection showed no significant difference depending on the length of exposure between the contact who had received injections and the source patient.[4]

6. Karelitz, S., and Karelitz, R. F.: The Significance of the Conditions of Exposure in the Study of Measles Prophylaxis, J. Pediat. 13:195, 1938.

Furthermore, our experience showed that a more intense exposure did not increase the secondary attack rate in a small group (9) of families in which susceptible contacts were exposed simultaneously to more than 1 patient with measles. This is in accord with the findings of Top in a large series of cases.[3e] It would seem, therefore, that the incidence of measles increases as the intimacy and the duration of exposure increase, until a saturation point is reached, after which further exposure does not affect the secondary attack rate. For intimately exposed family contacts, once the rash has appeared in the patient, hospitalization of the patient will neither lower the secondary attack rate of contacts who have not received injections nor increase the rate of protection of contacts to whom serum has been given.

In our experience only a relatively short period of exposure is apparently necessary for infection to occur in intimately exposed contacts. In the aforementioned schoolroom all 6 of 11 classmates who had never had measles contracted the disease after a thirty-five minute exposure. In a suburban boarding school 15 susceptible children who had been intimately exposed to a patient with measles for four hours were given a modifying dose of convalescent serum. In all these children modified measles developed.

The ideal method of calculating the incubation period of measles is to expose a susceptible child to a patient with measles in the preeruptive or early eruptive stage for a short time in a small room and then examine the contact daily until symptoms appear. Under these conditions the time of the infection and that of the onset of symptoms can be accurately determined. When exposure takes place in families under ordinary conditions, however, the time that infection occurs in susceptible children is not known, since the same patient may infect different contacts on different days and the onset of symptoms may not be noticed by an unobservant mother. Therefore the interval between the onset of the rash in the patient and that in the contact was considered a more practical guide for measuring the "incubation period" at home. In hospitals it is often difficult to determine accurately when the contact became infected, because the exposure is more varied and less intimate than in the home and there may be multiple sources of exposure. Nevertheless, there is an interesting agreement between the distribution of the incubation periods of measles arrived at by Stocks [7] from 2,490 records of home cases studied in the borough of St. Pancras in London from 1924 to 1928 by the same method employed by us and the distribution observed by Goodal [8] for 116 hospital cases.

Interest attaches to the variations in the incubation period. The mean length of this period was twelve days for the present series of contacts, with a range of ten to fourteen days for the great majority. The period was fifteen to nineteen days for one sixth of the contacts. The extremely long or extremely short periods of some contacts can be accounted for by the fact that measles is infectious for four to seven days and contacts may be infected on any one of these days. Variations in host resistance may also be responsible for differences in the length of the incubation period. Dudley calls the speed at which the rate of reception of successive small doses of infection overtakes the rate at which the immunizing power of the blood can deal with them the "velocity of infection." This may explain the tendency of the incubation period to be longer for the younger age groups, particularly for children between 12 and 23 months of age. The number of such children observed, however, is too small to warrant definite conclusions.

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7. (*a*) Stocks.[5] (*b*) Stocks, P., and Karn, M. N.: A Study of the Epidemiology of Measles, Ann. Eugenics **3**:390, 1928.

8. Goodal, E. W.: Incubation Period of Measles, Brit. M. J. **1**:73, 1931.

SUMMARY AND CONCLUSIONS

The secondary attack rate of measles in 266 intimately exposed susceptible family contacts 1 month to 14 years of age observed in the 1940-1941 epidemic in New York city was 75 per cent.

Age was the principal factor influencing the secondary attack rate of intimately exposed children. This attack rate was lowest for children in early infancy, highest for those 1 to 7 years of age (80 to 90 per cent) and sharply lower for those in the 10 to 14 year group (15 per cent).

Of 21 children 6 months to 10 years of age who escaped measles on one exposure and were reexposed, about one half contracted the disease.

Hospitalization of patients after the appearance of the rash did not lower the secondary attack rate of the intimately exposed susceptible children.

An increased intensity of exposure as measured by simultaneous contact of susceptible children with more than 1 patient with measles in 9 families did not increase the incidence of the disease.

The incubation period of measles was ten to fourteen days for 80 per cent of the contacts, fifteen to nineteen days for 14 per cent and less than ten days for 6 per cent. The proportion of patients with an incubation period of fifteen days or more was significantly greater in the 12 to 23 month age group.

Mr. Herbert H. Marks, of the Metropolitan Life Insurance Company, assisted in this work.

This study was made possible by the cooperation of Drs. Ralph Muckenfuss, Samuel Frant, Frank Calderone, Sophie Rabinoff and Franklin Foote and their respective staffs, of the New York City Health Department; of Miss Katherine Faville and her staff, of the Henry Street Visiting Nurse Service; of the medical boards of the Kingston Avenue and the Willard Parker Hospital, and by the pediatric department of the New York and the Bellevue Hospital.

Fifteenth Street and East River.

IMMUNITY TO TETANUS INDUCED BY A THIRD DOSE OF TOXOID THREE YEARS AFTER BASIC IMMUNIZATION

BASED ON A STUDY OF THIRTY-EIGHT ALLERGIC CHILDREN

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During the present emergency the subject of active immunization against tetanus commands special attention. Of particular importance is the degree of immunity induced by the stimulating, or "booster," dose of tetanus toxoid in relation to the interval between basic immunization and the administration of the "booster" dose.

In my first report,[1] on the appearance of tetanus antitoxin in the blood serum following two injections of 0.5 cc. each of combined alum-precipitated diphtheria and tetanus toxoids, it was shown that 94.6 per cent of a group of 186 allergic children attained a protective level of tetanus antitoxin when a critical level was considered as 0.01 American unit of antitoxin per cubic centimeter of blood. In a second study [2] a third, or "booster," injection of 0.5 cc. of the combined toxoids was given to 65 of the same 186 children. Nine of these 65 children had failed to attain adequate immunity after the first two doses of the combined toxoids. The "booster" dose was administered three to fifteen months after the completion of basic immunization. In a third communication [3] I reported the effect of "booster" injection of 0.5 cc. of combined diphtheria and tetanus toxoids or tetanus toxoid alone given to 31 others of the 186 children described in the first report two years after the completion of basic immunization. The "booster" dose of toxoid stimulated the production, in all instances, of an adequate titer for tetanus antitoxin. Moreover, the "booster" dose of toxoid given two years after the completion of basic immunization was always followed by a tetanus antitoxin titer which was higher and lasted for a much longer period than that which developed after basic immunization or after the "booster" dose of combined toxoids injected three to fifteen months after basic immunization.

In this communication, I am reporting the results of a comparable study on the degree and the duration of immunity after a "booster" injection of 0.5 cc. of the alum-precipitated toxoid given three years after basic immunization to 38 of the 186 children used in the study described in the first report. All of these 38 children

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F. G. Jones, of the Lilly Research Laboratories, gave technical assistance in this study.

From the Children's Allergy Clinic, Mount Sinai Hospital, Dr. Murray H. Bass, Director of the Department of Pediatrics.

The preparations of combined alum-precipitated diphtheria and tetanus toxoids and alum-precipitated tetanus toxoid used in this study were furnished by Eli Lilly & Co.

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had attained adequate immunity after the two initial doses of the combined toxoids. The children were divided into two groups. The 15 children in the first group were given a "booster" dose of 0.5 cc. of combined alum-precipitated diphtheria and tetanus toxoids, and the 23 in the second group were given a "booster" dose of 0.5 cc. of alum-precipitated tetanus toxoid alone. The creation of these two groups served a definite purpose which will be explained later. Since there was no appreciable difference in the immunities to tetanus induced by the combined toxoids and by the tetanus toxoid alone, the 38 children were treated as a single group for purposes of recording the antitoxin titers.

MATERIALS AND METHODS

The total number of samples of blood titrated for tetanus antitoxin from the 38 allergic children after the "booster" injection was 173. The dose consisted of 0.5 cc. of the alum-precipitated toxoids (either the combined diphtheria and tetanus toxoids or tetanus toxoid alone), and it was administered three years after completion of the basic immunization with two 0.5 cc. doses of the combined toxoids. Two hundred and fifty samples of blood had been titrated after the first two injections.

TETANUS ANTITOXIN TITERS AFTER THE SECOND AND AFTER THE THIRD, OR "BOOSTER," DOSE OF ALUM-PRECIPITATED TOXOIDS

Examination of the data reveals that for all 38 patients titers determined after the second dose of toxoid were available for comparison with the 101 which were obtained at intervals of one month to one year after the third, or "booster," dose. The values for antitoxin after the third dose of toxoid were higher in 94 of the 101 instances, lower in 2 and the same in 5. After the third dose the average antitoxin value was 12 times the average corresponding titer after the second dose. In the 2 instances in which the titers were lower after the "booster" dose of toxoid than after basic immunization, the former values were 2 units and 1 unit and the latter 3 and 2 units, respectively.

From the data on 36 children it was found that when initial tests made within two months after the "booster" dose showed the antitoxin values to be higher after the third dose than after the second, then tests performed one year later revealed not only that the drop of the titer was retarded after the third dose but that the antitoxin values were distinctly higher (a ratio of 14.5 to 1 or an average antitoxin titer of 0.641 unit as compared with 0.044 unit).

ANTITOXIN TITER WITHIN ONE MONTH AFTER THE "BOOSTER" DOSE OF TOXOID

Data from which to determine the effect of the "booster" dose of toxoid on the antitoxin response, with reference to the antitoxin titers obtained after the second and immediately preceding the third dose of toxoid, were available for 38 patients. These patients were divided into two groups.

The first group consisted of 17 children who had adequate antitoxin levels soon after the second dose of toxoid but whose titers some months later dropped to the level of 0.003 unit per cubic centimeter of serum. After the third dose of toxoid the titers of these patients ranged from 0.2 unit to 2 units, with an average titer of 1.13 units. The increase in titer ranged from 66 to 666 times, with an average increase of 376 times.

The other group consisted of 21 patients who also had adequate antitoxin responses soon after the second dose of toxoid but whose subsequent titers, obtained some months later, though lowered, remained above the critical level for protection against tetanus. After the third dose of toxoid the titers for 20 of these patients

ranged from 1 to 10 units of antitoxin, with an average titer of 3.35 units as compared with an average titer of 0.042 immediately preceding the dose. The increase in the titer ranged from 20 to 299 times, with an average increase of 134 times. (The data for the remaining patient in this group were omitted in computing the averages because of the unusually high antitoxin titer of 40 units obtained within one month after the injection of the third dose of toxoid.)

The data obtained in this study corroborated the observation, reported in previous communications, that the antitoxin levels attained within one month after the administration of a third, or "booster," dose of toxoid varied with those present immediately preceding the "booster" dose. When the titer dropped to the inadequate level (0.003 unit of antitoxin) after having been adequate (0.01 unit or more of antitoxin), then the average titer following a third dose rose to 1.13 units of antitoxin. When the titer was always maintained at the adequate level after two doses of toxoid, then the titer following a third dose reached the highest value, with an average of 3.35 units of antitoxin. For the patients in whom the titer had dropped to an inadequate level a third dose of toxoid given three to fifteen months [2] or two years [3] after the second injection induced antitoxin values about the same as those reported in the present study; the ratios were 1.3:1 and 0.8:1, respectively. For those patients who had maintained adequate titers the antitoxin value obtained when the third dose of toxoid was given after three years was higher than those obtained by giving it three to fifteen months or two years after the second injection; the ratios were 2:1 and 1.5:1 respectively.

TIME OF OCCURRENCE OF THE MAXIMUM ANTITOXIN RESPONSE

To determine the maximum antitoxin response following the "booster" dose of toxoid, two or more tests were done on each patient within three months after the injection. Seven days after the third dose the antitoxin titers per cubic centimeter of serum were as follows: 0.017 unit, 1 child; 0.05 unit, 2 children; 0.1 unit, 1 child; 0.2 unit, 6 children; 0.5 unit, 6 children; 1 unit, 5 children; 2 units, 12 children; 5 units, 4 children, and 10 units, 1 child. These results indicated that adequate tetanus antitoxin levels (0.1 unit or more) were obtained seven days after the injection of a booster dose of 0.5 cc. of either the combined alum-precipitated diphtheria and tetanus toxoids or the alum-precipitated tetanus toxoid alone in 92 per cent of the children who were treated three years after the completion of basic immunization. For 20 of the patients the antitoxin titer was at its maximum seven days after the administration of the toxoid, while for the remaining 18 patients the titer was at its maximum within one month. For the former group of 20 children the maximum antitoxin levels were as follows: 0.2 unit, 1 child; 0.5 unit, 2 children, and 1 to 5 units, 17 children. For the latter group of 18 children the maximum antitoxin levels were as follows: 0.5 unit, 4 children; from 1 to 5 units, 12 children; 10 units, 1 child, and 40 units, 1 child.

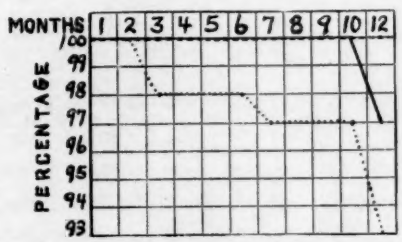
The foregoing observations confirm the results recorded in the two earlier studies on comparable groups of children who received the "booster" injection of toxoid three to fifteen months and two years after basic immunization. However, higher maximum antitoxin values were obtained after the third dose of toxoid for the majority of the children in the present series. In the group of children receiving the third dose within three to fifteen months after basic immunization titers which were adequate for protection were attained by all of the children within one month after the "booster" dose of toxoid. However, the groups of children given the third dose of toxoid two and three years after basic immunization attained adequate titers within seven days. For the majority of

the children in all three groups the antitoxin titers were at maximum level on the seventh day after the "booster" dose of toxoid was administered, and for every patient the maximum was reached within two months or less.

RATE OF DECLINE OF THE ANTITOXIN TITER TO AN INADEQUATE LEVEL

All of the 38 children tested in the present study acquired adequate tetanus antitoxin levels within one month after the "booster" dose of toxoid. The percentage of children who had a drop of antitoxin titer from an adequate to an inadequate level (0.003 unit per cubic centimeter of serum) and the number of months required for this change are shown in the chart. Thirty children were available for testing one year after the "booster" dose was administered. For purposes of contrast, there is also shown in the chart one curve constructed from the data for the group of 30 children who received the third dose of combined toxoids or of tetanus toxoid alone two years after the second injection and another for the group of 59 children who received the third dose three to fifteen months after basic immunization.

Examination of the chart shows that when the "booster" dose of toxoid was given three years after basic immunization 100 per cent of the 36 children main-



Percentages of 38 allergic children (broken line) who had achieved adequate immunity to tetanus (0.01 unit or more of antitoxin per cubic centimeter of blood serum) within one month after a third, or "booster," dose of either combined alum-precipitated diphtheria and tetanus toxoids or alum-precipitated tetanus toxoid alone given three years after basic immunization, of a parallel group of 59 allergic children (dotted line) who received a "booster" dose of combined toxoids three to fifteen months after immunization and of another parallel group of 30 allergic children (solid line) who received a "booster" dose of combined toxoids or tetanus toxoid two years after basic immunization.

tained adequate immunity for a year. In contrast, of the 30 children given the "booster" dose two years after basic immunization, 100 per cent maintained adequate immunity for ten months and only 97 per cent for a year. Of the 59 children given the "booster" dose three to fifteen months after basic immunization, 100 per cent maintained adequate immunity for two months, 98 per cent for six months, 97 per cent for ten months and only 93 per cent for a year. The group given the "booster" dose three years after basic immunization was the only one in which every child maintained adequate immunity against tetanus during the one year period. This is of importance when one considers that there is no cutaneous test available for the determination of immunity to tetanus and that the titration of blood serum for tetanus antitoxin is not a practical laboratory procedure. Moreover, the average antitoxin levels one year after the "booster" dose for the three groups of children were as follows: 0.373 unit of antitoxin per cubic centimeter of blood serum for the group of children given the "booster" dose of toxoid three years after basic immunization (1 patient had 10 units of antitoxin

and these data were purposely omitted in calculating the average titer since the inclusion of so high a titer would cause a distortion of the average); 0.298 unit of antitoxin for the group of children given the "booster" dose of toxoid two years after basic immunization, and 0.083 unit for the group of children administered the "booster" dose three to fifteen months after basic immunization.

*Maximum Tetanus Antitoxin Titer of Allergic Children and Titers Obtained Less Than One Year (When the Titer Dropped to 0.003 Unit of Antitoxin per Cubic Centimeter of Blood Serum) and One Year After the Third or "Booster" Injection of Combined Alum-Precipitated Diphtheria and Tetanus Toxoid**

Maximum Antitoxin Titer	Patients		Less Than One Year 0.008†		Antitoxin Titer, Units per Cc. of Serum, After Injections of Toxoid: One Year															
					0.008		0.01‡		0.05		0.1		0.2		0.5		1 or More		0.01 or More	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Booster Dose Given Between Three and Fifteen Months After Basic Immunization																				
0.01‡	1	2	1	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.1	3	5	1	33	0	0	2	67	0	0	0	0	0	0	0	0	0	0	2	67
0.2	9	16	0	0	2	22	5	55	1	11	1	11	0	0	0	0	0	0	7	78
0.5	18	32	0	0	0	0	8	45	4	22	6	33	0	0	0	0	0	0	18	100
1.0 or more	25	45	0	0	0	0	6	24	4	16	7	28	7	28	1	4	0	0	25	100
Total	56	100	2	4	2	4	21	37	9	16	14	25	7	12	1	2	0	0	52	93
Booster Dose Given Two Years After Basic Immunization																				
0.5	2	7	0	0	0	0	0	0	0	0	2	100	0	0	0	0	0	0	2	100
1.0 or more	28	93	0	0	1	4	0	0	3	11	4	14	10	36	8	29	2	7	27	96
Total	30	100	0	0	1	3	0	0	3	10	6	20	10	33	8	27	2	7	29	97
Booster Dose Given Three Years After Basic Immunization																				
0.2	1	3	0	0	0	0	1	100	0	0	0	0	0	0	0	0	0	0	1	100
0.5	6	17	0	0	0	0	1	17	3	50	2	33	0	0	0	0	0	0	6	100
1.0 or more	29	80	0	0	0	0	1	3	4	14	4	14	8	28	7	24	5	17	29	100
Total	36	100	0	0	0	0	3	8	7	20	6	17	8	22	7	19	5	14	36	100

* Data are included only for those children whose titrations were performed within forty days after the injection of toxoid. Data for the 56 children given a "booster" dose of toxoid between three and fifteen months after basic immunization and for the 30 children given injections two years after basic immunization were obtained in previous studies (footnotes 2 and 3). Twelve of the 30 children who received a "booster" dose two years after basic immunization and 15 of the 36 children given injections three years after basic immunization were given tetanus alum-precipitated toxoid alone. All percentages are approximate.

† Data for patients with an antitoxin titer of 0.008 unit less than one year after the "booster" dose are included because such titers persist at this level for at least two years.

‡ Patients with antitoxin levels of 0.017 and 0.025 unit are grouped with those having a titer of 0.01 unit.

INITIAL MAXIMUM ANTITOXIN LEVEL COMPARED WITH THE LEVELS ONE YEAR AND LESS THAN ONE YEAR AFTER THE THIRD DOSE OF TOXOID

Thirty-six of the 38 children were available for retesting one year after receiving the "booster" dose of toxoid. In the table the maximum antitoxin titers obtained within the first month and the titers obained one year after the administration of toxoid (or less than one year in those cases in which the titer dropped to the inadequate level earlier than this) are compared. The table also gives the comparable data for the children who received the third dose of toxoid three to fifteen months after basic immunization and for those who received it two years after basic immunization.

Four per cent of the 56 children who received a "booster" dose of toxoid three to fifteen months after basic immunization and none of those who received it two and three years after basic immunization showed a drop in titer from a level adequate for protection to an inadequate level in less than one year.

At the end of one year the level of antitoxin was maintained at 0.1 unit per cubic centimeter of serum in 72 per cent of the children who were given the third injection three years after the second dose (group *A*), in only 39 per cent of those who were given the "booster" dose three to fifteen months after basic immunization (group *B*) and in 87 per cent of the children who received the injection two years after basic immunization (group *C*). The ratios of about 2:1 between groups *A* and *B* and 0.8:1 between groups *A* and *C* are largely the result of the differences in initial maximum titers. Ninety-seven per cent of the children of group *A* as compared with 77 per cent of the children of group *B* and 100 per cent of the children of group *C* had maximum initial titers of 0.5 unit or more of antitoxin. Thus, it can be observed that the antitoxin titer had dropped to an inadequate level in one year or less in 8 per cent of the group of 56 children who were given the "booster" dose of toxoid three to fifteen months after basic immunization, in 3 per cent of the group of 30 children who were given the "booster" injection two years after basic immunization and in none of the group of 36 children who were given the "booster" injection three years after basic immunization.

REACTION AND SENSITIVITY

For the first 15 of the 38 children in the present series the "booster" dose consisted of combined diphtheria and tetanus toxoids. Ten of these 15 children had local reactions, similar to those described in a previous publication.[1] Five of these 10 children, of whom 3 had severe local reactions and 1 a moderate and 1 a mild reaction, some hours after the injection of the combined toxoids experienced elevations of temperature ranging up to 102 F., which lasted one day. The incidence of febrile reactions in this group of 15 children, 33 per cent, contrasts with 22 per cent in the group of 18 children given combined toxoids two years after basic immunization and with 3 per cent in the group of 65 children given combined toxoids three to fifteen months after basic immunization. One child of the group of 15 showed a general allergic reaction after the third injection of combined toxoids, with only a slight reaction at the site of the injection. The symptoms of the general reaction were an elevation of temperature to 101 F., severe headache which lasted for one day and severe hay fever commencing one hour after the injection and lasting for two days. This was the second allergic systemic reaction encountered in the active immunization of 186 allergic children who have had two to five doses of combined toxoids, including 36 children who have had a third dose of alum-precipitated tetanus toxoid alone, that is, in a total of 509 injections (an incidence of 0.4 per cent).

The remaining 23 of the 38 allergic children were given a "booster" dose of only alum-precipitated tetanus toxoid. None of these children showed a febrile reaction after the injection. However, 2 children experienced a moderate and 3 a severe local reaction.

The scratch tests, performed with undiluted combined diphtheria and tetanus alum-precipitated toxoids and with tetanus alum-precipitated toxoid alone, did not produce positive reactions, immediate or delayed, in any of the children observed in this study. The tests were performed prior to and from one to five months (an average of two months) after the third dose of toxoid. In view of these negative reactions to cutaneous tests with toxoid preparations, the systemic reactions (elevation of temperature, headache and hay fever) after the administration of the

"booster" dose of the combined alum-precipitated diphtheria and tetanus toxoids can be attributed to the increased sensitivity to the protein of the diphtheria bacillus rather than to the proteose contained in the toxoid preparation. In view of the increased incidence of systemic reactions following a "booster" dose of combined alum-precipitated diphtheria and tetanus toxoids (22 and 33 per cent, respectively, in the groups receiving it two and three years after basic immunization) it is advisable to employ alum-precipitated tetanus toxoid only, especially when the "booster" dose is given to older children two or more years after the completion of basic immunization with two doses of the combined toxoids.

COMMENT

The capacity to respond with maximum antitoxin levels to a stimulating, or "booster," dose of either combined alum-precipitated diphtheria and tetanus toxoids or alum-precipitated tetanus toxoid alone given three years after basic immunization with two 0.5 cc. doses of the combined toxoids is clearly shown by the results obtained with 38 children.

The results obtained in the present study confirm the observation, reported in three previous studies, that the intervals between the two basic doses of the combined toxoids and between these and the third, or "booster," dose have a direct influence on the antitoxin response. The longer the intervals (within the limits of the investigations to date) between the injections of toxoid the higher the antitoxin response. In the second study [2] the third and second doses of combined toxoids were given at intervals of three to fifteen months, in the third study [3] they were given at an interval of two years and in the present study at an interval of three years. The vast majority of the children in the last group responded with the highest antitoxin values thus far obtained. The influence of an interval of four years between basic immunization and the "booster" dose of toxoid is under investigation.

SUMMARY AND CONCLUSIONS

Three years after the completion of basic immunization with two 0.5 cc. doses of combined alum-precipitated diphtheria and tetanus toxoids, 38 allergic children were given a third, or "booster," dose of 0.5 cc. (15 children received combined alum-precipitated toxoids and 23 children alum-precipitated tetanus toxoid alone). The level of antitoxin was determined at various intervals after the second and after the third dose of the toxoids, and the respective totals of 250 and 173 specimens of blood serum were titrated for tetanus antitoxin.

An elevation of temperature which lasted one day followed the administration of the third dose of combined toxoids in 33 per cent of the children. This incidence of febrile reactions contrasts with 22 per cent in the group of 18 children given a third injection of combined toxoids two years after basic immunization, with 3 per cent in another group of 65 children given a third injection of combined toxoids three to fifteen months after basic immunization and with 1 per cent in the group given only the basic immunization.

One systemic allergic reaction (hay fever and severe headache) occurred in a child given the combined toxoids.

Prior to and from one to five months (an average of two months) after the "booster" dose, reactions to scratch tests with undiluted combined alum-precipitated diphtheria and tetanus toxoids and with alum-precipitated tetanus toxoid alone were negative.

The injection of a third, or "booster," dose of combined alum-precipitated diphtheria and tetanus toxoids or of alum-precipitated tetanus toxoid alone into allergic children three years after the completion of basic immunization with two doses of combined toxoids was followed within one month in all instances by an adequate tetanus antitoxin titer. This titer was always higher and lasted for a much longer period than that which followed basic immunization as well as that which followed a "booster" dose of combined toxoids given three months to two years after basic immunization. The antitoxin titer obtained on the seventh day after the administration of a "booster" dose of toxoid given three years after basic immunization was always adequate, and it was at its maximum at this time in the majority of instances.

Finally, when a child has had basic immunization with two doses of combined alum-precipitated diphtheria and tetanus toxoids and a third injection of toxoid is administered three years later, then alum-precipitated tetanus toxoid alone should be used in order to keep local and systemic allergic reactions at the minimum level.

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SUBCLINICAL VITAMIN DEFICIENCY

VI. THIAMINE IN SKELETAL MUSCLE OF INFANTS AND CHILDREN

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Thiamine occurs in skeletal muscle in two phases, extracellular and intracellular. The extracellular is probably freely diffusible and is in equilibrium with the thiamine of the plasma.[1] It is not of great concentration, the concentration in plasma being about 0.004 mg. per cubic centimeter. The concentration of intracellular thiamine is considerably greater, the content in whole muscle of an adult being about 0.5 mg. per gram.[2] The thiamine of muscle is thus almost entirely intracellular, being combined with protein and enzymatically active.[3] Earlier work[4] has suggested that the thiamine content of muscle in children may exceed that of muscle in adults. As a preliminary to settlement of this point, a further series of analyses of muscle of infants and children has been undertaken to determine the approximate range and variation of concentrations of thiamine in muscle in the lower age groups.

METHOD

Samples of skeletal muscle of 0.2 to 1.0 Gm. were obtained at autopsy or were removed from the abdominal musculature in the course of major operations. Samples were placed in tightly stoppered, weighed tubes, the weight was determined, and the muscle was homogenized by the Potter technic[5] in 0.02 molar sodium acetate–acetic acid buffer, p_H 4.6, a short time after collection. Aliquots of the homogenized sample were taken for analysis for thiamine and phosphorus. All analyses were made in duplicate or triplicate. Experiments for recovery of phosphorus and thiamine showed complete recovery of added material. The content of thiamine was determined by the yeast fermentation method.[6] Correction for yeast-stimulating substances other than thiamine was obtained by repeating the fermentation measurements on another set

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This investigation, while incomplete, has been terminated because of war work.

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From the Laboratory of Dental Medicine, Harvard School of Dental Medicine and the Department of Surgery, Harvard Medical School.

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of duplicate aliquots in which the thiamine had been destroyed by sodium sulfite.[7] The "true" thiamine content was calculated by difference.

The content of phosphorus was determined by the Kuttner-Lichtenstein technic.[8] Since the values for phosphorus depend almost entirely on the amount of intracellular phosphate present in muscle, measurements of phosphorus can be used to estimate the quantity of intracellular phase present in a given sample of muscle.

RESULTS

The data on the thiamine content of muscle taken from infants and children are summarized in table 1.

Table 2 is an excerpt from table 1 containing the data on those subjects whose diet was known at the time of biopsy. All were essentially afebrile, and all were

TABLE 1.—*Thiamine Content of Skeletal Muscle of Infants and of Children*

Patient	Age	Sex	Total Yeast-Stimulating Activity *	Activity After Sulfite Treatment *	"True" Thiamine *	Phosphorus, per Cent	Comments
A	Premature fetus †	..	1.47	0.14	1.33	....	
B	2 days	M	1.95	0.48	1.47	0.21	Imperforate anus
C	2 days	F	1.26	0.40	0.86	0.18	Intestinal obstruction
D	8 months	M	1.09	0.24	0.85	0.16	Abscess of wall of the chest
E	15 months	M	0.82	0.39	0.43	0.15	Bronchiectasis
F	27 months	M	1.57	....	....	0.15	Chronic nutritional disturbance
G	3 years	F	0.65	0.21	0.44	0.20	Celiac disease; ? intestinal obstruction
H	5 years	M	0.83	0.17	0.66	0.14	Urethral obstruction
I	5 years	M	0.60	0.00	0.60	0.18	Renal stone
J	6 years	M	0.54	0.33	0.21	0.16	Urethral obstruction
K	6 years	M	0.99	0.22	0.77	0.16	Urethral obstruction
L	7 years	F	0.65	....	....	0.20	Meningocele

* Expressed in thiamine equivalents, milligrams per gram of fresh muscle.
† Autopsy specimen. Biopsies of all other patients were taken at surgical procedures.

TABLE 2.—*Thiamine in Muscle of Children and Infants Taking "Good" Diets*

Patient	Age	Sex	Thiamine *
D	8 months	M	0.85
E	15 months	M	0.43
G	3 years	F	0.44
H	5 years	M	0.66
I	5 years	M	0.60
J	6 years	M	0.21
K	6 years	M	0.77

* Milligrams per gram of fresh muscle.

taking a "good" diet. The low value for patient E was unexplained. Patient G had been taking 2 teaspoons of a vitamin B complex preparation daily for some period. However, he suffered from celiac disease, and the amount of thiamine absorbed is questionable.[10] Patient J was taking sulfathiazole at the time of biopsy. The effect of sulfathiazole on analyses by the yeast fermentation procedure was not determined.

7. Schultz, A. S.; Atkin, L.; Frey, C. N., and Williams, R. R.: Application of the Sulfite Cleavage of Thiamin to the Yeast Fermentation Method, J. Am. Chem. Soc. **63**: 632, 1941.

8. Kuttner, T., and Lichtenstein, L.: Micro Colorimetric Studies: II., J. Biol. Chem. **86**:671, 1930.

9. Schultz, A. S.; Atkin, L., and Frey, C. N.: The Determination of Vitamin B_1 by the Yeast Fermentation Method, J. Indust. & Engin. Chem. (Anal. Ed.) **14**:35, 1942.

10. May, C. D.; McCreary, J. F., and Blackfan, K. D.: Notes Concerning the Cause and Treatment of Coeliac Disease, J. Pediat. **21**:289, 1942.

COMMENT

The variations observed in the thiamine content of skeletal muscle appear to exceed the variations in phosphorus content and may therefore be taken as true variations in intracellular concentration of thiamine. The concentrations of thiamine found in the fetus and in the younger infants are in general greater than those observed in the older children and in adult patients, but considerable deviation from this rule can be noted. It is difficult to be certain that part of this variation is not nutritional rather than an effect of age *per se*.

It should be noted that, contrary to earlier impressions based on a few studies of muscle in adults,[11] the amount of yeast-stimulating activity remaining after treatment with sodium sulfite is by no means negligible in samples of muscle taken from children. This point should be reinvestigated in a series of analyses of muscle of adults.

SUMMARY AND CONCLUSION

The thiamine content of skeletal muscle was determined in a group of infants and children by the yeast fermentation method of assay for thiamine. Correction was made for yeast-stimulating material other than thiamine by destroying the thiamine in the muscle with sodium sulfite and repeating the fermentation measurement. The "true" thiamine content of the samples of muscle was then calculated by difference.

In 12 subjects, ranging in age from a premature fetus to a 7 year old child, the concentration of thiamine varied between 0.21 and 1.47 mg. per gram of fresh muscle. In general, the higher values were found in the younger children and the fetus. Only 3 values were below 0.6 mg. per gram. Two of these low values were explainable on nutritional or technical grounds.

In infants and young children, concentrations of thiamine in the muscle below 0.6 mg. per gram of fresh muscle are probably abnormal.

Merck and Company supplied the thiamine used in this investigation.

300 Longwood Avenue (Dr. Gross).

11. Carleen and others.[6b] Schultz and others.[9]

HYPERVITAMINOSIS A AND CAROTENEMIA

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The effect on man of the ingestion of large amounts of carotene has been the subject of many articles in the past twenty years. On the other hand, knowledge of the results of overdosage with vitamin A is almost entirely confined to the effects on rats and mice. The lack of experience with hypervitaminosis in man is easy to understand, since only artificial concentrates contain sufficient vitamin A to be dangerous, and the ability to obtain these is limited. Early recognition of the possible danger of hypervitaminosis has limited the employment of excessive amounts in therapy. Moreover, the zone of safety between an adequate prophylactic dose and a dangerous dose is very large. One safeguard is lacking, that against the zeal of a person who is "sold on" vitamins. We have recently observed a case in which enthusiasm for vitamin therapy was present in a mother and eventually in her child.

REPORT OF A CASE

History.—B. B., a 3 year old boy of Jewish parentage, had appeared well up to the fall of 1938, when he was about 18 months old. At that time his appetite diminished and he seemed to be disinclined to play. Six months later (May 1939) he had a severe attack of tonsillitis, for which he was given sulfanilamide for two days. Two months after this, July 26, 1939, he had a tonsillectomy followed by hemorrhage, after which he received three transfusions. A blood count done after the hemorrhage showed severe anemia and 2,900 white cells per cubic millimeter, of which 44 per cent were neutrophils. The patient's liver and spleen were found to be enlarged, and clubbing of the fingers was noted. At this time he lost much of his hair, and that which grew back was sparse, dry and coarse.

During the next eight months, the child failed to improve, and because of the enlarging spleen and the continuing anemia he was admitted to the Harriet Lane Home for study with the tentative diagnosis of Gaucher's disease (March 1940).

Physical Examination.—When the patient entered the hospital in March 1940, his hair was sparse, dry and rather coarse, and eyebrows and fine hair over the body were lacking. The fingers and toes were slightly clubbed. He was pale and sallow, but there was no increase in pigmentation and no jaundice and the scleras were clear. The heart and lungs showed no abnormality. The liver was felt 2 cm. below the costal margin, the edge being sharp and firm. The spleen was enlarged and firm and was palpable 3 cm. below the costal margin. The child's height was 89 cm. (about normal for his age).

This study was aided by the John Howland Memorial Fund.

From the Department of Pediatrics of the Johns Hopkins University School of Medicine and the Harriet Lane Home of the Johns Hopkins Hospital.

Laboratory Data.—Most of the laboratory data are summarized in table 1. In addition, a test of dextrose tolerance gave the following results: fasting level, 81 mg. per hundred cubic centimeters of blood; levels after ingestion of dextrose, one-half hour 152 mg., one hour 168 mg., two hours 140 mg. and three hours 111 mg. The results (in milligrams per hundred cubic centimeters of blood) in the levulose tolerance test were: fasting, 91; half-hour, 132; one hour, 131; two hours, 105, and three hours, 102. The erythrocyte sedimentation rate (corrected) was 6 mm. in one hour on one occasion and zero on two others. The bromsulphalein test of hepatic function showed no retention of the drug. Excretion of urobilin was not increased in either the stools or the urine. The Wassermann and tuberculin tests gave negative reactions.

Roentgenograms of the chest and skull showed no abnormalities, but those of the limbs revealed considerable irregularity in cortical structure. In the phalanges and metacarpals the cortex was extremely thin and the medullary cavities appeared to be "vacuolated." The epiphyses of the upper ends of the humeri and tibias were mottled in appearance, and the distances between epiphyses and diaphyses were greater than normal. There were five carpal centers of ossification, indicating that skeletal development was in advance of the child's age in years.

A biopsy was done on a piece of bone, but unfortunately the tissue used was from the tibia, in which no change was disclosed by roentgenographic examination; as a result we are unable to say what was the nature of the abnormal process which occurred predominantly in the upper extremities. It is, however, possible to state definitely that the marrow showed no evidence of hypoplasia, nor was there any accumulation of reticuloendothelial cells. The only abnormality was a predominance of the more immature cells of the myeloid series. It was noted that the bones became decalcified in the fixative more rapidly than usual, but there was no evidence from the biopsy of any process that might cause decalcification of the bone.

Course.—The one outstanding feature of the examination that appeared to point to a possible etiologic factor was the enormously high content of vitamin A in the serum such as would not ordinarily be encountered except four to six hours after ingestion of an excessive dose of vitamin A. On questioning the mother, it was learned that beginning at 2 to 3 months of age the child had received a teaspoonful of halibut liver oil a day (about 240,000 U. S. P. units of vitamin A) up to the present time. Moreover, he had on occasion drunk the oil directly from the bottle in undetermined amounts.

As soon as it was appreciated that the case might be one of hypervitaminosis, the child was discharged with instructions that he should not be given any extra vitamin-A. Improvement was immediate. Within two months, the appetite had improved, the patient had gained weight and his hair had begun to grow back normally. By the end of six months his appearance and the composition of his blood were normal and the vitamin A content of the serum was within the upper limit of normality. Certain features remained, however; the phosphatase was still elevated and the serum proteins were still depressed. For a time after he was discharged from the hospital the child showed a desire for

butter and carrots, which led to a considerable though temporary increase in serum carotene and a temporary increase in serum lipids.

Two and a half years after leaving the hospital, the child was to all external appearances normal and of average height and development. He had had no illness except measles, and there was nothing in the mother's account to indicate that any pathologic change was still present. However, his liver was palpable as a firm sharp edge about 2 cm. below the costal margin; the spleen was felt as a large, firm mass occupying the upper left quadrant of the abdomen, and his fingers were still slightly clubbed. The laboratory data were essentially normal except for a slight elevation of the phosphatase content of the blood. The bones appeared normal in structure, but skeletal development was slightly in advance of the chronologic age (7 carpal centers of ossification at 5½ years of age).

In order to understand the significance of the conditions observed in this case, it will be necessary to review in considerable detail what is known concerning overdosage with vitamin A and its precursor, carotene. It has seemed best to carry out the review in the following order: (*a*) the known results of overdosage with vitamin A and carotene as determined by experiments on animals; (*b*) carotenemia as it is observed clinically, including the factors influencing the accumulation of carotene in the blood and the clinical effects of carotenemia, (*c*) hypervitaminosis, (1) the factors leading to accumulation of vitamin A in the blood and (2) the possible mechanisms the body employs to protect itself against the harmful effects of overdosage with vitamin A.

TABLE 1.—*Laboratory Data for Patient with Hypervitaminosis A*

Date	7/26/39	1/29/40	3/7/40	3/19/40	4/6/40	4/10/40	4/15/40	6/21/40	10/14/40	10/31/42
Erythrocytes, number/cu. mm.	2,100,000	3,800,000	4,300,000	3,900,000	...	3,400,000	...	4,400,000	4,600,000	6,000,000
Hemoglobin, Gm./100 cc.	7.5	8.0	10.1	11.0	...	10.1	...	11.3	12.0	11.2
Leukocytes, number/cu. mm.	2,900	6,100	6,200	4,600	...	4,800	...	5,700	8,400	7,200
Neutrophils, %	44	40	36	38	...	40	...	68	67	66
Lymphocytes, %	51	54	58	62	...	59	...	30	31	33
Monocytes, %	5	0	2	0	...	1	...	1	1	1
Eosinophils, %	0	1	4	0	...	0	...	1	1	0
Reticulocytes, %	..	..	..	2	...	...	...	...	...	..
Platelets, number/cu. mm.	..	..	..	68,000	...	70,000	...	34,000	42,000	120,000
Fasting blood sugar, mg./100 cc.	..	..	..	81	...	..	...	..	..	..
Serum nonprotein nitrogen, mg./100 cc.	..	..	..	21	...	..	...	..	..	..
Serum protein, %	..	..	..	4.3	...	5.0	...	3.8	5.6	..
Albumin, %	..	..	..	2.9	...	3.6	...	2.6	3.5	..
Globulin, %	..	..	..	1.4	...	1.4	...	1.2	2.3	..
Fibrinogen, %	..	..	..	0.58	...	...	...	...	...	..
Serum bilirubin (van den Bergh), mg./100 cc.	..	..	..	1.6	...	1.4	...	1.4	1.6	1.0
Serum calcium, mg./100 cc.	..	..	..	10.6	...	10.6	...	9.7	9.6	10.2
Inorganic phosphorus, mg./100 cc.	..	..	..	5.3	...	3.1	...	5.0	4.7	..
Phosphatase, Bodansky units	..	..	..	18.7	...	15.5	...	23	20	9.1
Serum cholesterol, mg./100 cc.	..	..	..	251	...	...	...	243	242	...
Serum total lipid, mg./100 cc.	..	..	..	1,140	800	...	770	950	840	430
Serum vitamin A, U. S. P. units/100 cc.	..	..	..	910	650	...	450	480	280	40
Serum carotene, micrograms/100 cc.	..	..	..	110	100	...	100	250	150	100

RESULTS OF OVERDOSAGE WITH VITAMIN A AND CAROTENE IN ANIMALS

As has been said above, knowledge of hypervitaminosis A is confined to the effects in animals, particularly in rats and mice, which are especially sensitive to the toxic effects of overdosage with vitamin A. Since different species vary greatly in degree of sensitivity to vitamin A and also possibly in the type of change produced by excessive amounts, one must be cautious in applying the knowledge gained by experimentation with animals to the interpretation of occurrences in the human being. There are, however, certain changes that have occurred in all the species tested, and these should form the basis for an understanding of the effects of intoxication with vitamin A. The following account will be based on the effects of excessive doses of vitamin A on the rat, since that animal has been most extensively studied.

When rats are given toxic doses of vitamin A (over 15,000 units a day), they lose weight almost immediately and may die in a week or ten days. There are certain rather constant symptoms; the hair, especially about the head, becomes unkempt and falls out and the skin becomes greasy and has a peculiar odor suggestive of hydrous wool fat. Later the eyes become sore, there is a bloody secretion from the nose and diarrhea develops.[1] These symptoms along with the extreme loss of weight and frequent loss of use of the posterior extremities provide a superficial resemblance to vitamin A deficiency. An almost constant feature is the development of multiple spontaneous fractures

1. (*a*) Domagk, G., and von Dobeneck, P.: Virchows Arch. f. path. Anat. **290**:385, 1933. (*b*) Moll, T.; Dalmer, O.; von Dobeneck, P.; Domagk, G., and Laquer, F.: Arch. f. exper. Path. u. Pharmakol. **170**: 176, 1933. (*c*) von Drigalski, W.: Klin. Wchnschr. **12**:308, 1933. (*d*) Bomskov, C., and Seemann, G.: Ztschr. f. d. ges. exper. Med. **89**:771, 1933. (*e*) Davies, A. W., and Moore, T.: Biochem. J. **28**:288, 1934. (*f*) Baumann, C. A., and Moore, T.: ibid. **33**:1639, 1939. (*g*) Noetzel, H.: Ztschr. f. d. ges. exper. Med. **105**: 83, 1939.

of the bones of the extremities.[2] Some investigators reported exophthalmos,[3] the cause of which is unknown; others stated specifically that they had never seen this result.[2f]

Histologically two features stand out, rarefaction of the bones with extreme thinning of the cortex [4] and increased deposition of fat in the reticuloendothelial cells, especially in the Kupffer cells of the liver and in the spleen.[5] There has been considerable disagreement over the degree of accumulation of fat and the extent of the hyperplasia of the reticuloendothelial cells; some investigators reported almost none,[5e] while one author likened the histologic picture to that observed in cases of Schüller-Christian disease.[2d]

Other histologic changes were noted by various authors, some of which may be of considerable significance if confirmed. Some authors, for instance, found evidence of increased activity of the thyroid gland [6]; one stressed increase in the basophilic cells of the anterior lobe of the hypophysis,[7] and hypertrophy of the island tissue of the pancreas was reported by another.[8]

Although the anatomic studies have usually been made on severely intoxicated animals, certain of the changes, especially those in the reticuloendothelial cells, are known to occur also in animals less severely poisoned. This fact indicates that such changes are the result not of a general intoxication but of a process more specifically associated with excess of vitamin A. Investigations of the relationship of overdosage with vitamin A to fat metabolism tend to confirm this suggestion. Since this subject has recently been reviewed,[9] it need only be touched on here.

When vitamin A in large but nontoxic daily doses was given to rats, guinea pigs or rabbits, a rise in cholesterol and in total lipids of the serum occurred.[10] This rise was only temporary, however, and tended to disappear after a time, even while the large doses of vitamin A were being given.[11] The same effect was observed in human beings [12] but not in dogs.[10c] In rats previous deficiency intensified and prolonged the response,[9] and a similar reaction was seen after pneumonia in infants receiving vitamin A.[13] Apart from this lipid reaction, the effect of vitamin A on physiologic processes has been little studied. No effect was observed on the formation of blood in animals.[14] The serum calcium and phosphorus were not affected, though there was an increase in excretion of calcium, which was attributed to "decalcification" of the bones.[1d] The basal metabolic rate was decreased.[15] An observation of considerable significance, if confirmed, was that function of the liver was at first improved and then depressed by excessive vitamin A.[16] All authors are agreed on the fact that recovery is prompt when the excessive intake of vitamin A is discontinued.

In contrast to the harmful results of overdosage with vitamin A, toxic effects have not been seen in animals after ingestion of excessive amounts of carotene; the animals have not lost weight or died and have not shown any of the outward manifestations of hypervitaminosis.[17] The changes in the metabolism of fat and the histologic changes in the reticuloendothelial "system," especially the increase in the storage of fat, are the same after the ingestion of carotene

2. (*a*) Bomskov and Seemann.[1d] (*b*) Davies and Moore.[1e] (*c*) Baumann and Moore.[1f] (*d*) Collazo, J. A., and Rodriguez, J. S.: Klin. Wchnschr. **12**:1768, 1933. (*e*) Strauss, K., and Ziegl, B.: Beitr. z. path. Anat. u. z. allg. Path. **94**:345, 1934. (*f*) Weslaw, W.; Wronski, B.; Wroblewski, A., and Wroblewski, B.: Klin. Wchnschr. **17**:777, 1938.

3. (*a*) Noetzel.[1g] (*b*) Strauss and Ziegl.[2e] (*c*) Collazo, J. A., and Rodriguez, J. S.: Klin. Wchnschr. **12**:1732, 1933. (*d*) Josephs, H. W.: Personal observation.

4. (*a*) Bomskov and Seemann.[1d] (*b*) Strauss and Ziegl.[2e] (*c*) Wolbach, S. B., and Bessey, O. A.: Physiol. Rev. **22**:233, 1943.

5. (*a*) Domagk and von Dobeneck.[1a] (*b*) Noetzel.[1g] (*c*) Collazo and Rodriguez.[2d] (*d*) von Drigalski, W., and Laubmann, W.: Klin. Wchnschr. **12**:1171, 1933. (*e*) Uotilla, U., and Simola, P. E.: Virchows Arch. f. path. Anat. **301**:523, 1938.

6. Uotilla, U.: Virchows Arch. f. path. Anat. **301**: 535, 1938.

7. Cornil, L.; Chevallier, A.; Paillas, J. E., and Chouquet, J.: Ann. d'anat. path. **16**:83, 1939.

8. Cornil, L.; Chevallier, A., and Paillas, J. E.: Ann. d'anat. path. **16**:74, 1939.

9. Josephs, H. W.: Bull. Johns Hopkins Hosp. **71**: 265, 1942.

10. (*a*) Collazo, J. A.; Torres, I., and Rodriguez, J. S.: Klin. Wchnschr. **13**:1678, 1934. (*b*) Jusatz, H. J.: ibid. **13**:95, 1934. (*c*) Wendt, H.: ibid. **14**:9, 1935. (*d*) Chalier, J.; Jeune, M.; Simon, F., and Alocoque, P.: Compt. rend. Soc. de biol. **129**:605, 1940.

11. (*a*) Josephs.[9] (*b*) Wendt.[10c]

12. (*a*) Wendt.[10c] (*b*) Jusatz, H.: Deutsche med. Wchnschr. **60**:573, 1934. (*c*) Lasch, F.: Klin. Wchnschr. **13**:1534, 1934.

13. Josephs, H. W.: Studies in Vitamin A: Vitamin A and Total Lipid of Serum in Pneumonia, Am. J. Dis. Child. **65**:712 (May) 1943.

14. Bomskov, C., and Sievers, G.: Ztschr. f. d. ges. exper. Med. **89**:780, 1933.

15. Chevallier, A., and Baert, H.: Compt. rend. Soc. de biol. **116**:1037, 1934.

16. Ikogaki, I.: Ztschr. f. Vitaminforsch. **9**:1, 1940.

17. (*a*) Moll and others.[1b] (*b*) Davies and Moore.[1e] (*c*) Chevallier, A.; Cornil, L., and Combe, R.: Compt. rend. Soc. de biol. **118**:574, 1935. (*d*) Lewis, J. T., and Reti, L.: ibid. **118**:577, 1935.

as after large but nontoxic doses of vitamin A.[18] The most obvious reasons for the less pronounced effects with carotene are: (*1*) carotene is less well absorbed than vitamin A; (*2*) the effect of carotene is seen only after conversion to vitamin A, and the time taken for this conversion would prevent the flooding of the body with the active vitamin which is necessary for the production of toxic effects. This subject will be more fully discussed in the section devoted to the body's defense against hypervitaminosis.

CLINICAL CAROTENEMIA

Factors Influencing the Carotene Level of the Blood.—1. Diet: Recognition of the primary importance of diet in carotenemia came as the result of the work of Palmer[19] and van den Bergh[20] and of a large number of clinical observations, most of them on children and persons with diabetes. These studies revealed correlations of xanthosis of the skin with increased content of lipochrome[21] in the blood and with diets rich in lipochromes (carotenoids).[22] Carrots are the primary food associated with carotenemia; also important are squash,[22g] oranges[23] and egg yolk[24] (egg yolk supplies xanthophyll rather than carotene). Xanthosis of dietary origin is most common in the late summer,[22e] and a number of observers have noted that the carotene of the blood is normally at a higher level at this time of the year.[25] In the cases reported in pediatric clinics, young infants appeared to be spared; the condition is observed only in later infancy and early childhood.[26] It is generally recognized that carotenemia and xanthosis are slow to develop, and relatively slow to recede after the high intake of carotene is discontinued.[27] Not every one reacts in the same way to the same diet, and it has been observed that some persons who acquire xanthosis easily do so on a surprisingly small extra amount of carotene.[22j] Moreover, the reactions of the same person may vary; it has been noted that a carotene-rich diet may cause xanthosis at first but that the yellow color may later disappear not to return during continuance of the diet.[28]

2. Level of Serum Lipids: The suggestion was made early that the serum lipids might have something to do with the development of carotenemia. The conditions other than ingestion of diets high in carotenoids under which carotenemia occurs in human beings are in general those associated with hyperlipemia—diabetes, nephrosis[29] and hypothyroidism.[28b] In cases of diabetes of the type in which the serum lipids are increased there is also a tendency for carotenemia to develop.[30] Rabinowitch[30e] reported

18. (*a*) Wendt.[10c] (*b*) Ralli, E. P.; Pariente, A. C.; Brandaleone, H., and Davidson, S.: Effect of Carotene and Vitamin A on Patients with Diabetes Mellitus, J. A. M. A. **106**:1975 (June 6) 1936. (*c*) Ocana, T.: Compt. rend. Soc. de biol. **120**: 267, 1935. (*d*) Stern, K., and Willheim, R.: Ztschr. f. d. ges. exper. Med. **97**:354, 1935.

19. Palmer, L. S.: Carotenoids and Related Pigments, New York, Chemical Catalogue Company, 1922.

20. van den Bergh, H.; Muller, P., and Broekmeyer, J.: Nederl. tijdschr. v. geneesk. **2**:127, 1920.

21. The terminology in this field is confusing. "Lipochrome" refers only to a colored substance associated with fat and is the older term. The early recognition and the importance of carotene among the lipochromes has led to the gradual use of the term carotenoids to designate this class of substances, all the members of which have similar chemical structures. In most clinical work "carotene" is used to designate anything that gives a yellow color in the purified benzine (petroleum ether) layer above an alcohol-water mixture. This is an incorrect use of the term but does no harm as long as the fact is recognized. "Carotenemia" is a term introduced by Hess and Meyers to include the entire clinical picture of yellow skin and increase of carotene in the blood; as such it has been widely accepted. It must be recognized, however, that the yellow color of the skin is not due to the carotene content of the blood, and, although there is a relationship, it is not always a close one. There is now a tendency to distinguish between "carotenemia" (excessive carotene in the blood) and "xanthosis cutis" (yellowness of the skin). As in the case of the faulty use of "carotene," the use of "carotenemia" to cover the entire syndrome does no harm, but it is well to recognize the possibilities for confusion.

22. (*a*) Hess, A. F., and Myers, V. C.: Carotinemia: New Clinical Picture, J. A. M. A. **73**:1743 (Dec. 6) 1919. (*b*) Kaupe, W.: München. med. Wchnschr. **66**: 330, 1919. (*c*) Klose, E.: ibid. **66**:419, 1919. (*d*) Stoeltzner, W.: ibid. **66**:419, 1919. (*e*) Ryhiner, P.: Jahrb. f. Kinderh. **94**:225, 1921. (*f*) Kohn, B.: Ztschr. f. d. ges. exper. Med. **36**:447, 1923. (*g*) Hashimoto, H.: Carotinoid Pigmentation of Skin Resulting from Vegetarian Diet, J. A. M. A. **78**:1111 (April 15) 1922. (*h*) Miyake, I.: Arch. f. Dermat. u. Syph. **147**:184, 1924. (*i*) Greene, C. H., and Blackford, L. M.: M. Clin. North America **10**:733, 1926. (*j*) von Drigalski, W.: Ztschr. f. Vitaminforsch. **3**:37, 1934. (*k*) Clausen, S. W., and McCoord, A. B.: J. Pediat. **13**:635, 1938.

23. (*a*) Miyake.[22h] (*b*) Josephs, H. W.: Personal observation.

24. (*a*) Stoeltzner.[22d] (*b*) Clausen and McCoord.[22k]

25. (*a*) Clausen and McCoord.[22k] (*b*) Catel, W.: Monatschr. f. Kinderh. **73**:316, 1938. (*c*) Kimble, M. S.: J. Lab. & Clin. Med. **24**:1055, 1939.

26. (*a*) Kaupe.[22b] (*b*) Stoeltzner.[22d] (*c*) Kohn.[22f]

27. (*a*) Clausen and McCoord.[22k] (*b*) Kauffman, F., and von Drigalski, W.: Klin. Wchnschr. **12**:306, 1933. (*c*) Heymann, W.: Carotinemia in Diabetes, J. A. M. A. **106**:2050 (June 13) 1936.

28. (*a*) Klose.[22c] (*b*) Umber, F.: Klin. Wchnschr. **53**:829, 1916.

29. (*a*) Wendt.[10c] (*b*) Clausen and McCoord.[22k] (*c*) Josephs, H. W.: Personal observation.

30. (*a*) Wendt.[10c] (*b*) Umber.[28b] (*c*) Labbé, M.: Presse méd. **33**:17, 1925. (*d*) Rabinowitch, I. M.: Canad. M. A. J. **18**:527, 1928; (*e*) Carotinemia and

that those patients with the highest levels of serum carotene tended in general to have the highest levels of lipid. If a large enough number of cases is studied to obtain the extreme variations in values which are encountered only under pathologic conditions, it can be shown that a correlation does exist.[31] However, the lack of demonstrable correlation in small series and under normal conditions has led several observers to deny that the lipids have any significance in carotenemia.[32]

In a recent study, it was found that during and after pneumonia, the levels of carotene and of lipid could be correlated when account was taken of the ingestion of carotenoids and the time required after ingestion for accumulation of the carotenoids in the blood. When carotene was given by mouth the rate of accumulation in the blood stream depended in general on the level of lipid during the period of ingestion.[13] In a recent study of hypothyroidism the values of serum carotene were found to be dependent on those of the serum lipid.[33] A close relationship between carotene and cholesterol has been stressed, and it has been claimed that the yellow color of the nodules present in xanthoma is due to their content of carotene.[34]

3. Other Factors: The fact that when carotenoids are removed from the diet the carotene of the serum falls to an extremely low level suggests that the stores of carotene in the fat depots are only to a minimal extent available for maintenance of the level in the blood. Moreover, it has been found that thin people have a higher concentration of carotene in the fatty tissue than well nourished persons,[38a] which indicates that even when fat is mobilized from depots in the tissues, carotene remains behind. The fate of the carotene which disappears from the blood is not entirely known. Some of it is evidently deposited in the fatty tissues. A large part is removed from the circulation in the liver, where it undergoes conversion to vitamin A. Some of it is undoubtedly oxidized. Whether or not it has any function other than as a precursor of vitamin A is unknown.

The increase in the activity of the reticuloendothelial cells after the ingestion of excess carotene may explain why the high initial carotenemia tends to disappear later; the rate at which removal is accomplished is at first exceeded by the rate of intake but later increases to take care of the excess carotene. It has been suggested that hypothyroidism [35] and diabetes [36] interfere specifically with the conversion of carotene to vitamin A, but it is hard to see how this would lead to accumulation of carotene in the blood unless the mechanism of removal were also impaired. Several investigators have advanced the hypothesis that failure of oxidation of carotene is the determining factor, especially in diabetes and hypothyroidism.[37] Until more is known concerning the part that oxidative processes play in the removal of carotene from the blood in the living organism, and not merely in vitro, this hypothesis can hardly be proved or disproved.

Carotenemia has been noted among Europeans living in the tropics, and Castellani and Chalmers [38] mentioned a condition which they called ochrodermatosis, which occurred only at sea level and disappeared when the patients were removed to higher altitudes. The diet was not mentioned. Sequeira [39] saw what he considered a similar case in Africa apparently not dependent on diet and without hypercholesteremia. Improvement occurred only after the patient was given small amounts of thyroid. Bounin and Lévinson [37c] reported carotenemia in a group of patients with chronic malaria who had been inadequately treated.

Effects of Carotenemia.—Xanthosis Cutis: Carotenemia has been considered completely harmless, its only symptom being the development of the characteristic yellow color of the skin which generally disappears as soon as the responsible conditions have been corrected. Usually the yellow color varies with the level of carotene in the blood, but a close parallelism is not always present. A striking exception to the general rule is the absence of xanthosis cutis in persons with carotenemia with nephrosis

Diabetes: Relationship Between Sugar, Cholesterol and Carotin Contents of Blood Plasma, Arch. Int. Med. **45**:586 (April) 1930. (*f*) Barbudo, N., and von Querner, F.: Wien. Arch. f. inn. Med. **30**:279, 1937.

31. Josephs, H. W.: Bull. Johns Hopkins Hosp. **65**: 112, 1939.

32. (*a*) Ralli, Pariente, Brandaleone and Davidson.[18a] (*b*) Bürger, M., and Reinhardt, A.: Deutsche med. Wchnschr. **45**:430, 1919. (*c*) Ralli, E. P.: Brandaleone, H., and Mandelbaum, T.: J. Lab. & Clin. Med. **20**:1266, 1935.

33. Josephs, H. W.: To be published.

34. (*a*) Thomson, J. G.: Ztschr. f. d. ges. exper. Med. **92**:692, 1934. (b) Bennhold, H.: Klin. Wchnschr. **13**:36, 1934.

35. Fasold, H., and Heidemann, L. R.: Ztschr. f. d. ges. exper. Med. **92**:53, 1933.

36. (*a*) Ralli, Pariente, Brandaleone and Davidson.[18b] (*b*) Ralli, Brandaleone and Mandelbaum.[32e]

37. (*a*) Heymann.[27e] (*b*) Stannus, H. S.: Internat. Clin. **1**:146, 1929. (*c*) Bounin, E., and Lévinson, M.: Ztschr. f. Vitaminforsch. **5**:12, 1936.

38. Castelllani, A., and Chalmers, A. J.: Manual of Tropical Medicine, ed. 3, London, Baillière, Tindall & Cox, 1919.

39. Sequeira, J. H.: Brit. J. Dermat. **49**:69, 1937.

(Clausen and McCoord [22k] and personal observations). Histologic examination shows that the carotene is found mostly in the superficial horny layer of the skin and that its concentration becomes less the deeper one goes.[40] The fact that it is present in sweat and sebaceous material has led to the hypothesis that its presence in the skin is dependent on this excretion and the subsequent rubbing of the carotene into the horny layer. Its predominant occurrence in those areas in which the horny layer is particularly thick or in which sweating is most marked (palms and soles, forehead, nasolabial folds, axillas and groins) would tend to bear out this theory.

2. Increased Serum Lipids: Anderson and Soley [41] noted an increase in serum lipids and pronounced fall in basal metabolic rate in several California farmers who had eaten vegetables in large amounts. The liver was enlarged in 4 of the 9 patients. An increase in serum lipid was noted by two other observers [42] but, in general, little attention has been paid to the blood lipids in carotenemia.

3. Harmful Effects: Some recent work throws doubt on the generally accepted harmlessness of carotenemia. Sequeira [39] reported weakness, loss of weight and low blood pressure. He was speaking, however, of cases observed in the tropics in which diet was apparently not a factor; hence it is possible that the carotenemia was secondary to some underlying factor responsible for the whole condition. Anderson and Soley reported that the liver was enlarged in about half of their patients and that the removal of rose bengal from the blood was slower than normal.

A more certain example of harmfulness is furnished by a case recently reported by Henschen.[43] A woman of 49 acquired a pica-like craving for carrots during an attempt to cure "anemia" with a vegetable diet. She ate 2 to 3 bushels a month (about 2 pounds [0.9 Kg.] a day), mostly raw, for six months, and a generalized xanthosis cutis developed. She also complained of paresthesias of the hands and feet. She was thin, pale, rather easily fatigued and subject to dyspnea. The liver and spleen were enlarged. The yellow color was general over the body, but the scleras were clear. Examination of the blood gave the following data: The hemoglobin content was 57 per cent. Erythrocytes numbered 3,400,000 per cubic millimeter and leukocytes 5,300, with neutrophils 62 per cent, lymphocytes 28 per cent and monocytes 4 per cent. There was poor clot formation, but no estimation of the number of platelets was made. There was 0.347 mg. of carotene per hundred cubic centimeters of serum (normal 0.07 to 0.19). Serum xanthophyll was not increased. When carrots were removed from her diet, the patient slowly improved, though the number of white cells remained low. Later cataracts developed.

Reports of Earlier Cases of Dietary Carotenemia.—In the records of the Johns Hopkins Hospital there are 6 cases of carotenemia in which the diet alone either was or might have been responsible. This series is exclusive of cases of carotenemia occurring in the course of diabetes or nephrosis or of hypothyroidism, in which the low thyroid function is definitely the primary factor. They are included at this point because they have a bearing on the discussion of hypervitaminosis and because they confirm the hypothesis that carotenemia may not be as harmless as heretofore pictured.

CASE 1.—The patient was a child of 16 months, who had recently come from California, where she had been indulged in oranges, the only source of carotene that she could be ascertained to have received in significant amount. She recovered promptly, and at no time did untoward symptoms develop.

CASE 2.—The serum of this patient, also a child, was received for diagnosis. All that I can ascertain is that no harm resulted from the carotenemia and that the clinical diagnosis was made from the yellow color of the skin. It is unusual to see xanthosis cutis with the serum carotene as low as it was in this case.

CASE 3.—Carotenemia was diagnosed in a well-to-do, asthmatic man who enjoyed vegetables in large quantities. No special studies were made, and the case is included only as one in which the patient was not harmed by the carotenemia.

CASE 4.—A 38 year old clergyman had as his only complaints yellowness of the skin and loss of weight. He had been supplementing his diet with carrots and carrot juice for about seven years. When carrots were removed from his diet, he recovered rapidly.

CASE 5.—This patient, a colored farmer who had lived largely on vegetables, especially spinach, was extremely undernourished. Low blood pressure, emaciation and extreme muscular weakness led to a first impression of hypopituitary cachexia (Simmond's disease). Later, hypothyroidism was suggested on the bases of the high serum cholesterol and low basal metabolic rate. On a diet of high caloric value he improved extraordinarily rapidly.

CASE 6.—A well-to-do woman of 45, because of imagined idiosyncrasies to meat, eggs, milk and starchy foods, had lived largely on vegetables and fruits for a number of years. In addition to having carotenemia, she was markedly underweight, with low blood pressure

40. (*a*) Hashimoto.[22g] (*b*) Miyaki.[22h] (*c*) Ansai, cited by Zechmeister, L.: Ergebn. d. Physiol. **39**:117, 1937.

41. Anderson, H. H., and Soley, M. H.: Am. J. M. Sc. **195**:313, 1938.

42. (*a*) Kohn.[22f] (*b*) Lian, C.; Abaza, A., and Sassier, R.: Bull. et mém. Soc. méd. d. hôp. de Paris **51**: 801, 1935.

43. Henschen, C.: Schweiz. med. Wchnschr. **71**: 331, 1941.

and asthenia. Hypothyroidism was diagnosed on two occasions when she was in the hospital. She was greatly improved by a diet high in calories, given in the hospital.

The patients in the first 3 of these cases were symptomless and entirely unharmed by the carotenemia. In case 1, however, the serum lipids were well above the normal. The last 2 cases considered by themselves would be hard to evaluate; in case 5 the extremely inadequate diet might have caused the entire clinical picture, and in case 6 the impression of hypothyroidism was particularly strong and in addition the diet was inadequate. Certainly the cases in which there is evidence of harm were those in which the patient had taken the carotene-containing foods for a long time or had lived largely on diet may have caused the low blood pressure, and in case 4 the blood pressure was not excessively low. The high values for blood lipid and cholesterol and the low basal metabolic rate are definitely part of the picture of carotenemia, occurring as they did in Anderson and Soley's cases as well as in 3 of the 4 cases reported here in which the lipids were determined. A tendency to leukopenia also appears to be a characteristic, but one that may be absent; in the series I have reported it occurred in 2 of the 3 cases with symptoms (4 and 6), and it was present in Henschen's case. Anderson and Soley merely stated that the blood was normal, without reporting the actual counts.

Perhaps the most confusing aspect is the relationship of carotenemia to hypothyroidism.

TABLE 2.—*Laboratory Data for Patients with Carotenemia*

Case No.	Age, Sex	Source of Carotene	Date	Serum Carotene, Micrograms/ 100 Cc.	Serum Vitamin A, U. S. P. Units/ 100 Cc.	Serum Lipids, Mg./ 100 Cc.	Serum Cholesterol, Mg./ 100 Cc.	Basal Metabolic Rate	Loss of Weight	Weakness	Hypotension	Leukocytes, No./ Cu.mm.	Comments
1	16 mo. F	Oranges	2/8/38	610	90	1,100	...	..	0	0	...	.....	
2	Child ?	Unknown	Jan. 1939	220	55	650	...	..	0	0	...	.....	
3	37 yr. M	Carrots	Oct. 1936	...	...	.....	...	..	0	0	...	8,500	Diagnosis made on appearance of skin
4	36 yr. M	Carrots and carrot juice for 7 years	9/12 9/22 12/10	600 420 150	60 100 120	1,410 970 720	441	—19	+	+	Slight	4,100	Symptomatic improvement on discontinuance of carrots and carrot juice
5	18 yr. M	Vegetables, especially spinach, principal source of food for 2 years	12/22	550	...	1,250	429	—45	++	++	++	6,800	Rapid improvement on high calory diet
6	47 yr. F	Vegetables and fruit principal source of food for 4 years	....	...	...	.....	Elevated	—45	++	++	+	4,100	Considered to be hypothyroid on 2 occasions, but improved rapidly on high calory diet

them. Case 4 is the link connecting the cases of innocuous carotenemia with those in which harm has resulted; in this case there is no doubt of the primary position of the carotenemia, and at the same time the patient showed loss of weight, asthenia, high blood lipids and cholesterol and a low basal metabolic rate.

From these cases plus those described by Anderson and Soley, of carotenemia in California farmers,[41] one may form a picture of the effects of carotenemia. Loss of weight is usual, but it is not possible to be certain to what extent this is the direct result of carotenemia and to what extent the result of the concurrent inadequacy of the diet. The same is true of muscular weakness. Hypotension is even more difficult to evaluate. It was not mentioned by Anderson and Soley. In case 6 of the series just described the low blood pressure antedated the abnormal diet; in case 5 the extreme inadequacy of the

Every symptom that has been mentioned as occurring with carotenemia except the loss of weight could occur in hypothyroidism. Only consideration of the fact that the diet came first and the symptoms followed will allow a correct evaluation to be made. A possible explanation of this similarity lies in the reported antagonism between carotene or vitamin A and thyroxin. According to this theory the symptoms of hypothyroidism may exist not only as the result of diminished activity of the thyroid gland, but as the result of "neutralization" of thyroxin by carotene or vitamin A.

Another point that must be emphasized is that it is the abnormal intake of carotene rather than the amount in the blood that is the cause of trouble. In conditions such as diabetes and nephrosis, in which carotenemia may occur without excessive intake, none of the symptoms cited are present. Apparently under ordinary condi-

tions carotene must be ingested in excessive amount for a long time or must form the major part of the diet to the exclusion of other constituents in order to be harmful.

CLINICAL HYPERVITAMINOSIS

Factors Influencing Vitamin A of the Blood.—Little is known of the factors leading to the increase of vitamin A in the serum, and that little has come principally from experimentation on animals.

1. Diet: Increasing the dietary intake of vitamin A beyond a certain optimum will increase the amount stored, but it is usually not possible to push the level of vitamin A in the blood above what might be called a normal maximum, except for a few hours after administration of a large dose. A child of 4 years who was given percomorph liver oil in large doses for resistant rickets received about 120,000 U. S. P. units of vitamin A every day for a month with no more than a minimal effect on her serum vitamin A, determined twenty-four hours after the last dose. Two infants were given 200,000 U. S. P. units of vitamin A a day for several weeks. There was a slight temporary rise in vitamin A in the blood, lasting about a week. Likewise, in rats ingestion of 2,500 U. S. P. units a day raised the level of vitamin A from 1 unit per cubic centimeter of serum to about 2 units, and, although a large amount was stored in the liver, the serum vitamin A fell to nearly its former level within two or three days after the high ingestion of the vitamin was discontinued.[44]

2. Level of Serum Lipids: The conditions in which hyperlipemia occurs tend to be associated with increases in vitamin A as well as with carotenemia. Also, as in the case of carotenemia, the relationship is of a general nature and one must utilize pathologic extremes to be able to demonstrate it.[31] An important difference lies in the far more rapid removal of excessive vitamin A than of carotene from the blood. The postabsorptive curve of vitamin A is influenced by the level of serum lipid just as is that of carotene [13] but the specific removal of vitamin A in the liver effectively prevents prolonged accumulation in the blood, while the slower removal of carotene permits an accumulation which is also aided by the relatively higher solubility of the latter substance in the blood lipids. It seems likely also that the solubility in lipids is a less important factor in the case of vitamin A than of carotene. If vitamin A and lipids tend to vary together, it is because they are subject to similar influences.[45]

The highest values for vitamin A seen in over 700 cases did not exceed 2.5 units per cubic centimeter except immediately after ingestion, even though the series included some cases with high levels of lipid (cases of nephrosis and 1 of myxedema). Following pneumonia there was a tendency for hyperlipemia to develop in some of the children observed; under these circumstances the vitamin A might temporarily reach a value of 3.5 units per cubic centimeter of serum (patients not receiving supplementary vitamin A). These levels were the highest seen with the exception of those in the case of vitaminosis reported here.

Protection Against Hypervitaminosis.—A factor of safety for the animals that rely on carotene for their source of vitamin A is the relative harmlessness of carotene. Also any damage which it does cause is apparently not permanent, and rapid and complete recovery is to be expected as soon as the excessive intake of carotene is stopped.

The facts just reviewed point to the existence of a mechanism for the maintenance of the level of vitamin A in the blood within certain limits. It seems highly significant that this mechanism exists in the case of the vitamin, which can produce toxic effects, and not in the case of its precursor, carotene, which appears to be relatively harmless. It is interesting that the dog, which apparently lacks this mechanism for the limitation of the level of serum vitamin A (personal observation), is the one animal thus far studied in which none of the toxic effects from vitamin A have been elicited.[10c]

Another protective mechanism is the storage of vitamin A in the liver, where it appears to be harmless. It is not the total amount of vitamin in the body that determines the presence of toxic symptoms but the ingestion of amounts large enough to overwhelm the ability of the liver to remove it from the circulation.[46] Seemingly it is possible to push the storage in the liver without limit, and no symptoms of intoxication are produced unless the daily dose is raised above the "toxic" limit. When vitamin A or carotene is given intravenously the excess is removed with great rapidity.[47] In this removal the cells of the reticuloendothelial system play a primary role, particularly the Kupffer cells of the liver. This

44. Josephs, H. W.: Bull. Johns Hopkins Hosp. **71**: 253, 1942.

45. Josephs.[9, 13]

46. (*a*) Davies and Moore.[10e] (*b*) Ikegaki, I.: Ztschr. f. Vitaminforsch. **7**:113, 1938.

47. (*a*) Drummond, J. C.; Gilding, H. P., and McWalter, R. J.: J. Physiol. **82**:75, 1934. (*b*) Groth, H., and Skurnik, L.: Acta med. Scandinav. **101**:333, 1939.

has been shown by fluorescence microscopy [48] as well as by "blockade" experiments.[49] The increase in activity of these cells under the influence of overdosage with vitamin A may therefore be looked on as a factor in the defense against hypervitaminosis.

When excessive vitamin A is given to rats over a period of time, a rise in the level of serum lipid occurs, which, however, is temporary. This has been taken as evidence that one of the fundamental effects of vitamin A is on the metabolism of lipids, but that ordinarily the effect is adequately and promptly compensated for. When the vitamin is suddenly introduced in large amounts the compensatory process is temporarily overcome and a rise in blood lipid occurs. It has been suggested that this compensatory process involves increased activity of the thyroid gland.[50] Support for this idea comes from the demonstration of antagonism between vitamin A and thyroxin.[33] The continuance of the high content of lipid in the serum in the cases of carotenemia cited in this paper suggests that this compensatory factor may be more effective in the rat than in man.

COMMENT ON THE CASE

From this review of reports of experimental and clinical carotenemia and hypervitaminosis A, one obtains some insight into the significance of certain pathologic changes in the case which is reported. However, since final proof of the mechanisms involved is lacking, the interpretations which follow must be looked on as suggestions rather than as demonstrations of the manner in which excessive vitamin A acts.

Abnormal Appetite.—Whether or not it is justifiable to label as "abnormal" a liking for an article of food which most people would not eat by choice, there is no doubt that the child's liking for halibut liver oil was a factor in the case which is reported. It is interesting that this desire for the oil was replaced by a desire for butter and carrots after the administration of the oil was discontinued, and that as the patient improved clinically he lost all such desires. Henschen's patient with carotenemia had developed such an appetite for carrots that she was impelled to search garbage cans to satisfy her craving. Two of Hashimoto's patients among Japanese peasants had an abnormal appetite for squash, the source of their carotene. Clausen and McCoord mentioned a case in which the patient had an abnormal craving for carrots; the serum carotene in this case was the highest in their series. These examples are cited to show that an abnormal appetite for carotene-containing foods may occur.

It is possible that the appetite existed first and was primarily responsible for the large intake, but it seems more probable that the increased intake was begun for economic or other reasons and that the abnormal appetite developed subsequently. Desire for some particular dietary constituent not infrequently results from the necessity of correcting a deficiency or some other condition, for example, the craving for salt in persons with adrenal insufficiency. It is conceivable that excessive vitamin A or carotene taken at first through economic necessity or zeal might give rise to changes that would create or increase the desire for the material that caused the changes. The change in desire from halibut liver oil to carrots and butter in our patient when use of the oil was stopped suggests that this was the case. It may be noted from table 1 that after the patient was discharged from the hospital the content of carotene in the serum rose for a short time to a definitely abnormal level, which confirms the history of increased intake of carotene.

Hepatomegaly and Splenomegaly.—The original impression of Gaucher's disease was suggested by the presence of a large liver and spleen together with anemia of the hypoplastic type. The roentgenograms of the bones were not indicative of this condition except that the changes in the metacarpals and phalanges suggested the presence of a process replacing normal marrow with pathologic tissue. The increased storage of fat in animals subjected to intoxication with vitamin A suggests the possibility that such storage may have occurred in our patient; however, we have no direct evidence of this or of any reticuloendothelial proliferation, at least in the bone marrow, though such a proliferation may account for the enlargement of the liver and spleen. The improvement of the patient when ingestion of excessive vitamin A was stopped is evidence that vitamin A intoxication was primarily responsible for the clinical picture. It may be pointed out in confirmation that Henschen's patient also had hepatomegaly and splenomegaly with a hypoplastic type of anemia, and that in the cases of carotenemia which I summarized the patients who had any symptoms tended to have leukopenia and a slight reduction in the number of red cells.

The idea that vitamin A and carotene are capable, under conditions that lead to accumulation in the blood, of causing a disturbance in the

48. Popper, H., and Brenner, S.: J. Nutrition **23**: 431, 1942.

49. Lasch, F., and Roller, D.: Klin. Wchnschr. **15**: 1636, 1936.

50. Wendt, H.: Deutsche med. Wchnschr. **62**:1213, 1936.

storage of lipids with certain features in common with the changes which occur in xanthomatosis, Gaucher's disease or Niemann-Pick disease is an attractive one. However, the reported effect of vitamin A on reticuloendothelial proliferation in animals has not yet been thoroughly confirmed, nor has it been shown that the splenomegaly or hepatomegaly in clinical cases is actually due to increase in the storage of lipids.

Increased Vitamin A in Serum.—The vitamin A of the blood of our patient when first seen was at a level which has otherwise been encountered only at the height of the postabsorptive curve, four to six hours after a relatively large dose. Not only that, but it remained at a high level after all excess ingestion of vitamin A had been stopped and only slowly returned to normal over a period of six months. As stated previously, attempts to cause a rise in serum vitamin A in other patients to more than a limited extent or over more than a limited time have proved unsuccessful. While this paper was in preparation a child of 8 months was brought to the outpatient department after receiving 3 teaspoons of percomorph liver oil a day during a period of four months (corresponding to about 500,000 U. S. P. units of vitamin A per day). The vitamin A of the serum was 110 U. S. P. units per hundred cubic centimeters and the total lipid 730 mg. per hundred cubic centimeters, both normal values. This case exemplifies the efficiency of the mechanism by which the constancy of the blood vitamin A is maintained and at the same time indicates that this mechanism in the patient whose case is reported here was seriously impaired.

In the discussion of the body's protection against hypervitaminosis the role played by the reticuloendothelial cells in removing vitamin A and carotene from the blood was cited. If, as has been suggested, the cells of the reticuloendothelial system are made more active by an overdose of vitamin A the vitamin would be more, not less, effectively removed from the blood. The fact that in the case under discussion the vitamin was less effectively removed indicates either that the child had some defect in his reticuloendothelial response or else that intense, prolonged overdosage is capable of injuring this response. The only work that I could find bearing on this point is that of Ikegaki,[46b] who found that in early stages of overdosage with vitamin A liver function increased, whereas later it decreased; the functions dealing with removal of dye from the blood stream and with detoxification were particularly affected. In our patient, bromsulphalein was removed normally but the serum bilirubin was consistently somewhat raised (1.6 mg. per hundred cubic centimeters). In Anderson and Soley's cases of carotenemia, 5 of the 8 patients tested showed impairment of the ability of the liver to remove rose bengal from the blood.

A second possibility in this case is that the limit of the liver's ability to store vitamin A was exceeded. While little is known of the capacity of the human liver, work on rats shows that when storage of vitamin A has been pushed to a high point the vitamin disappears with great rapidity when excessive intake is discontinued, supposedly by oxidation or some other form of destruction. Whether or not prolonged administration of vitamin A could impair this mechanism for getting rid of amounts in excess of the storage capacity is not known. As I have pointed out, however, excessive storage has little influence on the level in the blood, so that it would be difficult to explain the continuance in this patient of a high level over a prolonged period after the intake of vitamin A was discontinued, especially since the total amount in circulation is only a minute fraction of the amount in storage.

Increased Level of Serum Lipids.—The increase in lipid in the blood in the patient under discussion was definite though not excessive. (The normal range is approximately 550 to 750 mg. per hundred cubic centimeters, though higher may be encountered in otherwise normal persons.) The gradual fall after excessive intake of vitamin A was stopped leaves no doubt regarding the causation. The level of carotene in the patient's serum was not excessively high except on one occasion, as previously mentioned, just after his return home, when he had a craving for carrots and butter. It may be noted that on this occasion the content of lipids also increased slightly. A rise in blood lipids appears to be a significant part of the picture of hypervitaminosis A as well as of carotenemia. The cholesterol also takes part in the rise of lipids but in some cases, as in those reported by Anderson and Soley, the increase is not correspondingly great. The basal metabolic rate was not determined in the patient discussed with hypervitaminosis A, but it was decreased in most of my patients with carotenemia. In fact, the picture of carotenemia resembles that of hypothyroidism to such an extent that a distinction may be difficult. Only the definite association of the condition with a vegetable diet and its disappearance as soon as the source of carotene was removed lead to a correct diagnosis of carotenemia. The explanation for the similarity between the two conditions may lie in the vitamin A–thyroid antagonism to which reference was made previously, in which case the symptoms of hypothyroidism in carotenemia would be due to the presence of

an excess of thyroid antagonist and not to an actual diminution in the activity of the thyroid gland.

It was pointed out previously that the rise in lipids which occurs in animals subjected to continued excessive doses of vitamin A or carotene was a temporary phenomenon and that the return to normal levels was evidence of the development of a compensatory process. Wendt suggested that the compensation might involve an increase in thyroid activity.[10c] I have suggested that the continuance of the high level of lipids in the patient reported on here might also indicate that the "compensatory" process is less effective in man than in rats. The fact that the dose required to elicit the lipid response in man is relatively far smaller than that for rats [13] points in the same direction. If, as suggested, increased activity of the thyroid supplies the "compensatory" process, its relative failure in man might explain both the persistence of the high levels of serum lipid and the symptoms of hypothyroidism.

Skeletal Abnormalities.—The skeletal changes which occurred are difficult to evaluate, and the biopsy was of no aid. The speed of decalcification was in line with the observation that in animals decalcification of bones is one of the most constant effects of hypervitaminosis. The most outstanding features in the roentgenograms of the patient were the evidences of a more rapid epiphysial development, the irregularities, the apparent stippled effect of the epiphysial centers, the increased distance between epiphysis and diaphysis and the advanced development of carpal centers of ossification. Even two and a half years after the removal of excessive vitamin A the carpal centers were in advance of the patient's chronologic age. The child, however, has not grown unduly and at present is no more than at the upper limit of normal stature for his age. It may be mentioned that Wolbach and Bessey [4c] in a recent review stated the opinion that vitamin A acts to increase the rate of development of bone; however, they gave none of the evidence on which the opinion was based.

Associated Abnormalities.—Four other abnormal conditions present in this case are worth noting. (*a*) The rise in serum phosphatase depends on the activity of processes which also give rise to changes in the bones, and it is to be considered in relation to these. Phosphatase is also increased in diseases of the liver, and, as has been pointed out, there is evidence of hepatic damage in this case. (*b*) The low level of serum protein, especially of the globulin fraction, is probably of considerable significance, but it cannot be evaluated in the present state of knowledge. (*c*) Sparse, coarse hair was a prominent characteristic of the clinical picture. Loss of hair by rats subjected to vitamin A intoxication has been a prominent feature of some descriptions. In the patient, the return of hair of normal texture and distribution was almost the first sign of improvement. (*d*) Clubbing of the fingers was a striking feature of the clinical picture when the child was first seen. It was still present though less prominent after two and a half years. Its significance is not known, but it may possibly indicate damage to the liver, since clubbing of the fingers and toes is not infrequently observed in cirrhosis in children.

The question of complete recovery of the patient in the case reported is still open. Clinically the child is well and has remained so during the past two years. The only causes for anxiety are the continued presence of splenomegaly and to a less degree of hepatomegaly and the persistent advance in skeletal development. In Henschen's case splenomegaly was slow to disappear and leukopenia persisted for at least a year. In view of the magnitude and the duration (three years) of the intake of vitamin A it would be surprising if some permanent change had not resulted. My fear is not so much that there may be a progressive process still active as that there may have been some scarring of the liver that will later give rise to trouble.

SUMMARY

Severe hypervitaminosis A occurred in a boy of 3 years who had received about 240,000 U. S. P. units of vitamin A daily since he was about 3 months of age. The condition was characterized by hepatomegaly, splenomegaly, hypoplastic anemia, leukopenia, increased serum vitamin A, increased serum lipids, advanced skeletal development, clubbing of the fingers and sparse, coarse hair; it was accompanied with an abnormal appetite for halibut liver oil, the source of the vitamin. Most of the symptoms cleared promptly when the excess vitamin A was removed from the diet.

Experimental and clinical observations indicate the existence of a mechanism for the maintenance of a constant level of vitamin A in the blood, possibly related to the activities of the reticuloendothelial cells. No such mechanism seems to exist for carotene. The occurrence of hypervitaminosis A in this child indicates either that some defect existed in the system responsible for the protective reaction or else that intense, prolonged overdosage is capable of injuring the regulatory mechanism.

Johns Hopkins Hospital.

Case Reports

TULAREMIC MENINGITIS

REPORT OF A CASE AND SUMMARY OF PREVIOUSLY REPORTED CASES

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Although evidence of meningeal irritation and involvement of the central nervous system is observed not infrequently in cases of tularemia which terminate fatally, instances in which invasion of the meninges by the infecting organism has been proved, either during life or at necropsy, are extremely rare. The case reported here represents an instance of tularemic meningitis occurring in a 5 year old child. While the patient was still living the infecting organism was isolated from the blood and spinal fluid. Necropsy confirmed the existence of a meningitis due to Bacterium tularense. The case is of interest also in that the mode of infection was unusual. The patient contracted tularemia from the bite of a cat. Because so few cases of tularemic meningitis are recorded in the literature, it is considered advisable to add this case. In addition to the present case, we shall give summaries of previously reported cases and postmortem observations.

In a discussion of the pathologic lesions of tularemia, in 1927, Francis and Callender [1] mentioned a case which was probably an example of tularemic meningitis. The patient, a Negro of unstated age, had suffered for several months from persistent swelling and suppuration of the axillary lymph nodes and had died after several days of stupor. The clinical diagnosis was tuberculous meningitis. Necropsy revealed acute bronchopneumonia and one minute apical fibrous tubercle. Numerous opaque, firm nodules were seen in the liver and spleen. The meninges were thickened and opaque over the lower portion of the brain. Microscopic examination of the meninges revealed a diffuse lymphocytic infiltration. The lesions may have been those of tuberculous meningitis, although tubercle bacilli could not be demonstrated by staining. No cultures of blood or inoculations of guinea pigs were made.

In 1931 Haizlip and O'Neil [2] reported a case of meningitis due to Bact. tularense occurring in a 45 year old white man. In this case the onset of meningeal symptoms occurred four days after the patient first noticed a painful, swollen lesion on the palmar surface of the left thumb and pain and swelling in the axilla. He had cleaned some rabbits and a squirrel nine days before the cutaneous lesion was noticed. When he was admitted to the hospital, the patient was prostrated. His neck was stiff, and moving his head caused great pain. The spinal fluid was cloudy and contained 2,100 cells per cubic millimeter, 70 per cent of which were polymorphonuclear leukocytes. Gram-stained preparations of the sediment from the spinal fluid revealed no organisms. Cultures of the blood and of the spinal fluid

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1 Francis, E., and Callender, G. R.: Tularemia: Microscopic Changes of the Lesions in Man, Arch. Path. **3**:577 (April) 1927.

2. Haizlip, J. O., and O'Neil, A. E.: A Case of Meningitis Due to Bacterium tularense, J. A. M. A. **97**:704 (Sept. 5) 1931.

were negative. The blood serum agglutinated Bact. tularense in a dilution of 1:40. Death occurred on the ninth day of the illness.

Necropsy revealed multiple pulmonary infarctions, local areas of necrosis in the spleen and early hepatic cirrhosis. Postmortem studies did not include examination of the brain. Attempts to infect a guinea pig with a piece of spleen taken at autopsy were unsuccessful.

The sediment from the spinal fluid was inoculated into a guinea pig, and at autopsy multiple minute areas of focal necrosis were seen in the animal's liver and spleen. Smears of the guinea pig's spleen, when stained after the method of Foshay, revealed numerous Bact. tularense organisms.

Bryant and Hirsch [3] in 1931 reported a case of tularemic leptomeningitis occurring in a 48 year old white man. This patient contracted ulceroglandular tularemia from contact with an infected rabbit. Nine days after exposure he became irrational, and nuchal rigidity developed. Kernig's and Brudzinski's signs were positive. The spinal fluid was cloudy and contained 400 cells per cubic millimeter, 84 per cent of which were mononuclear leukocytes. Bacteria were not found in the sediment from the spinal fluid, and cultures of the spinal fluid on the usual mediums were sterile. The patient's serum on the fourteenth day of illness agglutinated Bact. tularense in a dilution of 1:40. Death occurred on the sixteenth day of the illness.

Necropsy revealed miliary tularemic lesions of the liver, spleen and lungs. Examination of the brain revealed focal lesions of the leptomeninges, the adjacent portions of the brain, and the ependymal and subependymal tissues. The lesions were made up of an exudate of monocytes and polymorphonuclear leukocytes, with varying degrees of necrosis. Where the meningeal lesions encroached on the brain, the tissues of the latter were necrotic and infiltrated with exudate cells. Inoculation of guinea pigs with crushed spleen of the patient produced focal lesions characteristic of tularemia in the spleen, liver and lungs.

In 1932 Hartman [4] reported the occurrence of tularemic encephalitis in a white man. Four days after the patient had skinned rabbits, an ulcer developed at the base of his left thumb, accompanied with axillary adenitis, fever and malaise. Four days later he became delirious and his neck was stiff. When he was admitted to the hospital, four days later, he had definite nuchal rigidity and was aroused with difficulty. His serum agglutinated Bact. tularense in a dilution of 1:640. Examination of the spinal fluid on his eleventh day in the hospital revealed bloody fluid with 145 white cells per cubic millimeter. Cultures of the spinal fluid were negative. He died on the thirty-third day of his illness.

At necropsy areas of focal necrosis and of infiltration by polymorphonuclear leukocytes were observed in the lungs, peribronchial lymph nodes, spleen, liver and brain. The case was complicated by the presence of tuberculous lesions in one kidney and epididymis. Tubercle bacilli could be demonstrated only in the lesions in the involved kidney and epididymis. The author concluded that the case was one of tularemia with diffuse encephalitis and coexisting tuberculosis of the kidney and epididymis. No mention is made of any attempt to inoculate animals with material obtained at autopsy. The evidence of the existence of tularemia in this case rests on the clinical record, the high titer of the agglutinins for Bact. tularense in the patient's serum and the nature of the pathologic lesions.

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3. Bryant, A. R., and Hirsch, E. F.: Tularemic Leptomeningitis: Report of Case, Arch. Path. **12**:917 (Dec.) 1931.

4. Hartman, F. W.: Tularemic Encephalitis: Pathology of Acute Tularemia with Brain Involvement and Coexisting Tuberculosis, Am. J. Path. **8**:57 (Jan.) 1932.

Pund and Hatcher [5] in 1935 reported a case of tularemic meningitis occurring in a 12 year old Negro girl. The patient had been ill with fever, abdominal pain and headache followed by nausea and vomiting for two days, and when she was admitted to the hospital she was semicomatose. An ulcer 3 cm. in diameter was present on the left forearm. During eight days of observation she had high fever and semiconsciousness followed by coma. Tularemia was not suspected clinically, and agglutination for Bact. tularense was not determined. The spinal fluid was examined on the fifth day and was found to contain 114 cells per cubic millimeter. Cultures of the blood and of the spinal fluid were negative. Death occurred on the tenth day of the illness.

At necropsy areas of focal necrosis were observed in the spleen, liver, lungs and lymph nodes. Numerous small areas of focal necrosis were distributed over the surface of the brain. On microscopic examination these areas proved to be accumulations of small round cell and occasional polymorphonuclear leukocytes. Most of the lesions were just below the surface of the brain, but larger ones extended into the leptomeninges. The meninges showed diffuse infiltration with small round cells and polymorphonuclear leukocytes. Inoculations of animals with material obtained at autopsy were not done. Blood serum obtained at autopsy agglutinated Bact. tularense in a dilution of 1 : 1,280.

REPORT OF CASE

The patient, a 5 year old white girl, was admitted to the pediatric service of Vanderbilt University Hospital on Jan. 16, 1943. Five days prior to admission she had been bitten on the right hand by a cat which had been fed the uncooked viscera of wild rabbits on several occasions. The patient's past history and family history were noncontributory. The wound resulting from the bite was treated with kerosene and by soaking in a solution of magnesium sulfate. Two days before the child was admitted to the hospital, the lesion on her hand became red. However, she did not complain of pain until the following day, when she struck her hand against a table. At this time she noted a painful swelling in the right axilla. She complained of headache, and her temperature was 101 F. A few hours later her temperature rose to 103 F. and she had a shaking chill. During the night before admission she was delirious and began to vomit all feedings. Her physician prescribed sulfathiazole, but the medicine was not retained. Because of the progression of her symptoms, she was brought to the hospital.

When the patient was admitted to the hospital, she was observed to be acutely ill, poorly nourished, delirious and irrational. She expectorated frothy saliva almost constantly. Her temperature was 105 F. and her skin was hot, dry and loose. On the right thenar eminence there was a reddened, elevated, indurated lesion about 2 cm. in diameter, with a white, necrotic central area. There was no generalized lymphadenopathy, but a tender mass about 3 cm. in diameter was palpable in the right axilla. The overlying skin was not remarkable. The head was normal in contour and size. The eyes were normal in position and showed no paralysis of the intrinsic or extrinsic muscles, and the optic fundi appeared normal. The mucous membranes of the mouth were dry and dirty, and there was moderate hyperemia of the pharynx. There was no stiffness of the neck. Percussion revealed no indications of enlargement of the heart; the rate was rapid but regular, and no murmurs were heard. Examination by percussion and auscultation showed that the lungs were clear. The abdomen was scaphoid, and the margin of the liver was barely palpable. No other masses were felt. There was no demonstrable paralysis or weakness; the deep tendon reflexes were sluggish, and Kernig's and Brudzinski's signs were absent.

Laboratory studies at the time the patient entered the hospital revealed: hemoglobin, 13.5 Gm. per hundred cubic centimeters; red cell count, 5,200,000; white cell count, 17,000, with 80 per cent polymorphonuclear leukocytes, 15 per cent lymphocytes and 5 per cent monocytes. The results of urinalysis were negative except for a 3 plus response to the test for acetone. The blood gave a negative response to the Kahn test.

The wound at the base of the thumb was incised, and a small amount of purulent material obtained. Cultures were made of this material. Although the diagnosis of tularemia was

5. Pund, E. R., and Hatcher, M. B.: Tularemic Meningitis: Report of Case with Postmortem Observations, Ann. Int. Med. **10**:1390 (March) 1937.

considered, the possibility of a septicemia with some other organism could not be excluded, and administration of sulfathiazole was started. Cultures of blood obtained on the day of admission and on the third day in the hospital showed the presence of Bact. tularense. A few hours after the patient was admitted a petechial rash appeared on the chest and abdomen, and later it involved the proximal portions of the upper extremities. A lumbar puncture performed on the day of admission revealed clear spinal fluid with no cells and a normal content of sugar.

The patient was given a solution of dextrose intravenously. The next day she seemed much improved; she was rational and took feedings fairly well. However, during the following five days her condition remained about the same, and she continued to have high spiking fever with daily elevations of temperature up to 105 F. Numerous patchy, white necrotic areas developed on the buccal surfaces. Because there was no appreciable change in her clinical course, sulfathiazole was discontinued on the fifth day.

Bact. tularense was isolated from the wound on the thumb, and also from the blood and sputum at the time the patient was admitted to the hospital.

On the eighth day in the hospital the patient seemed to take a decided turn for the worse. She complained of vague abdominal pain; her temperature rose to 106 F.; she had abdominal distention, and her spleen became palpable. The following day she had persistent vertical nystagmus and slight stiffness of her neck and was drowsy. Because of the presence of meningeal signs a lumbar puncture was performed. The spinal fluid was cloudy and contained 2,000 cells per cubic millimeter, 99 per cent of which were lymphocytes. The content of sugar in the spinal fluid was 18 mg. per hundred cubic centimeters, and the reaction to Pandy's reagent was 4 plus. A culture of the spinal fluid contained Bact. tularense.

The patient was given 150 cc. of blood from a donor who had recovered from tularemia, and the next morning she seemed somewhat improved. A roentgenogram of the chest at this time showed no pulmonary involvement. The improvement was transient, however, and the following evening convulsive movements of the right arm and leg and labored and irregular respiration developed. She was placed in an oxygen tent but, in spite of this, exhibited gradually deepening cyanosis. She became comatose, and her temperature rose to 107 F. Respiration failed, and she died quietly on the thirteenth day of her illness.

Gross Pathologic Changes.—The body was that of a well developed and poorly nourished 5 year old white girl. It was still warm, and rigor mortis was firmly established in the muscles of the face. The head, eyes, ears, nose and mouth presented no significant abnormalities. On the right thenar eminence there was a circular, indurated, reddish area of ulceration approximately 1 cm. in diameter with greatly encrusted edges. The base was about 1 mm. in depth. The right axillary nodes were firm, nonfluctuant, easily palpable and about 3 cm. in diameter, but the epitrochlear glands on that side were not felt. There was no other significant adenopathy.

Peritoneal Cavity.—About 60 cc. of yellowish, turbid fluid was present in the peritoneal cavity. The peritoneal surfaces were moist, smooth and dull. The liver was enlarged, extending 4 cm. below the costal margin in the anterior axillary line. The spleen was enlarged, extending to the costal margin on the left. The omentum appeared normal and full of fat. The retroperitoneal lymph nodes were enlarged, firm, nonfluctuant and pinkish red.

Pleural Cavities.—There was 15 to 20 cc. of clear yellow fluid in each pleural cavity. The lungs were voluminous and pink. The mediastinum anteriorly was fatty; no enlarged lymph nodes were seen, and the pleural surfaces were smooth, shiny and glistening.

Pericardial Cavity.—A normal amount of straw-colored fluid was present in the pericardial sac, and the serosa was smooth, shiny and glistening.

Heart.—The heart weighed 80 Gm. The valves, endocardium and coronary arteries presented no significant abnormalities, but all of the chambers appeared to be dilated. The myocardium was brown and soft and flabby.

Thymus.—The thymus weighed 3 Gm. It was soft, pinkish white and well lobulated. The cut surface appeared normal.

Lungs.—The right lung weighed 260 Gm., the left, 220 Gm. These were air containing everywhere, but they felt boggy throughout; the cut surfaces were moist and purplish red. The bronchi were filled with an abundance of frothy fluid. The mucosa was pink, and no areas of ulceration were evident.

Gastrointestinal Tract.—The stomach was empty and well contracted. The mucosa throughout the intestinal tract presented a normal appearance. Bile could be expressed through the ampulla of Vater into the duodenum by pressure on the gallbladder. The mesenteric lymph nodes were enlarged, firm, nonfluctuant and pinkish red.

Liver.—The liver weighed 750 Gm. Numerous small white chalky nodules, which averaged 1 to 2 mm. in diameter, were seen beneath the capsule. The parenchyma was yellowish brown, and scattered over the cut surface were many soft chalky white nodules about 1 mm. in size. The gallbladder was small and appeared normal.

Spleen.—The spleen weighed 90 Gm. Its capsule was taut and smooth, and through it were seen many chalky white nodules, some of which were 2 mm. in diameter. The malpighian corpuscles appeared to be slightly larger than normal and were easily seen. Many nodules similar to those beneath the capsule were also seen on the cut surface. These nodules were irregular in outline and sharply demarcated from the purple pulp. From the centers of the larger nodules small amounts of yellow material could be scraped away.

Pancreas.—The pancreas weighed 40 Gm. and was of normal size, shape and consistency. There were numerous enlarged lymph nodes near it.

Adrenals.—The adrenal glands weighed 2.5 Gm. each. The usual markings were seen, but no areas of necrosis could be found.

Kidneys.—The right kidney weighed 40 Gm.; the left, 45 Gm. The usual markings were present, and no significant abnormalities were seen.

Pelvic Organs.—None of the pelvic organs presented significant lesions.

Bone Marrow.—The bone marrow removed from a vertebral body was moist and pink. The costochondral junctions of the ribs did not appear remarkable.

Brain.—The brain weighed 1,300 Gm. The calvarium was removed without difficulty, a tense, purplish dura mater being exposed. The dural sinuses appeared normal. There was a noticeable increase in the amount of slightly turbid, brownish cerebrospinal fluid, and the convolutions appeared to be slightly flattened. The meninges, especially over the sulci, had a ground glass appearance with numerous minute yellowish white nodules less than 1 mm. in diameter. These nodules were most prominent in the region of the lateral cerebral fissure on the left side and around the base of the brain. The meninges were much thicker and cloudier over the base of the brain than over the cortex. The ventricles appeared to be only slightly if at all dilated. The ependyma was finely granular, and the gross structure of the choroid plexus appeared normal. The pituitary gland weighed 0.5 Gm. and showed no significant lesions. The spinal cord was soft and boggy, and the meninges had a ground glass appearance, although no areas of necrosis could be seen by gross examination. No significant lesions were seen on the cut surfaces of any part of the central nervous system.

Lymph Nodes.—The lymph nodes in the right axilla were removed and were found to be matted together into a well circumscribed mass, about 3 cm. in diameter, which was nodular and pinkish yellow. From the cut surface a moderate amount of necrotic brownish yellow material escaped, leaving a deep, ragged crater around which many yellowish white soft nodules could be seen. A few thrombosed blood vessels were present. No normal lymphatic tissue could be detected. The lymph nodes from the pancreatic and retroperitoneal regions were discrete, firm and nonfluctuant. The cut surface showed mottled areas of yellowish white, uniform nodules, 1 mm. in diameter. The areas of caseation were neither as marked nor as large as those seen in the axillary nodes.

Histologic Changes.[6]—*Heart.*—There were extreme marked congestion and interstitial edema of the myocardium, but the endocardium and epicardium exhibited no significant changes. The aorta showed minimal perivascular infiltration by round cells, mainly of the lymphocytic type.

Thymus.—The lobules of the thymus were highly vascular, and many polymorphonuclear leukocytes were scattered throughout. The remainder of the thymic tissue presented no abnormalities.

Lungs.—Sections of the bronchioles showed areas of ulceration where fibrin and polymorphonuclear leukocytes persisted and walls heavily infiltrated with polymorphonuclear leukocytes and lymphocytes. The blood vessels were acutely engorged throughout. The pleura showed no evidence of inflammatory reaction. The alveoli were filled with coagulated serum, a small amount of fibrin, many polymorphonuclear leukocytes and a few large mononuclear phagocytic cells. No areas of focal necrosis were seen.

Gastrointestinal Tract.—A section through the pyloric ring of the stomach showed that the mucosal lining was intact; however, the superficial portions of the lamina propria showed

6. Tissues were fixed in a 10 per cent concentration of solution of formaldehyde U. S. P. and in Zenker's fluid, embedded in paraffin and routinely stained with hematoxylin and eosin, carbolfuchsin, erythrosin and toluidine blue. Sections failed to reveal any organism.

a pink, hyaline material containing a few thrombosed capillaries. A few polymorphonuclear leukocytes were scattered diffusely throughout the entire lamina propria. The remaining layers of the stomach did not appear remarkable, and the serosa showed no evidence of any inflammatory reaction.

Liver.—The capsule of the liver appeared to be normal. Scattered about in the parenchyma, with no regard to location, were many minute focal lesions whose centers stained bright pink and showed many pyknotic fragments of cells. Surrounding these was a zone of epithelioid cells. No Langhans cells were present; only a rare polymorphonuclear leukocyte was seen in the surrounding cellular zone, and the hepatic cells were granular due to cloudy swelling. There was considerable congestion of the sinusoids, but the endothelial cells lining the vessels were not remarkable.

Spleen.—The capsule was of normal thickness. The splenic pulp was greatly engorged and contained numerous scattered polymorphonuclear leukocytes and mononuclear phagocytic cells. The malpighian bodies appeared slightly larger than normal because of an increase in the number of large, clear mononuclear cells. The most conspicuous lesions were the single and conglomerate ones scattered throughout the pulp. The younger lesions showed a bright pink-staining area containing only a few necrotic cells with a peripheral zone of mononuclear cells and epithelioid cells. The older lesions had larger areas of caseation, and the surrounding zone showed a few more polymorphonuclear leukocytes than it did in the younger lesions, with large mononuclear phagocytes and lymphocytes. Only a few plasma cells were seen.

Pancreas.—The pancreas presented no significant lesions.

Adrenals.—Several small areas of necrosis surrounded by lymphocytes, epithelioid cells and mononuclear cells were seen in the reticular layer of the adrenals. The cortex showed more vacuolation than is normally seen and the parenchyma was markedly congested.

Kidneys.—The kidneys were congested and showed moderate parenchymatous degeneration. In the peripelvic adipose tissue there were several perivascular collections of lymphocytes and large mononuclear leukocytes but no areas of caseation or necrosis.

Urinary Bladder.—The urinary bladder showed no significant lesions.

Internal Genitalia.—A section from the fimbriated end of the fallopian tube showed collections of polymorphonuclear leukocytes and many necrotic cells in the lumen. The mucosal folds were moderately infiltrated with polymorphonuclear leukocytes, lymphocytes and large mononuclear cells, and the lymphatics were distended with lymphocytes and large mononuclear phagocytic cells. In the stroma beneath the serosa were found quite a few large, acidophilic mononuclear cells. The serosa was made up of a single layer of mesothelial cells without cellular reaction. The remainder of the internal genitalia showed no significant lesions.

Lymph Node.—The section taken from the right axillary mass showed complete destruction of the surrounding adipose tissue. There were multiple areas of caseation, many of which coalesced, with necrotic cellular elements scattered about. At the periphery there were many lymphocytes, epithelioid cells and large mononuclear phagocytic cells. Occasional multinucleated cells, but no cells of the Langhans type, were seen. Many blood vessels, both arteries and veins, were thrombosed, and the majority of the vessel walls showed areas of necrosis and infiltration with lymphocytes and large mononuclear cells. Sections through the nodes about the pancreas and the retroperitoneal nodes showed younger lesions with more normal architecture. The sinuses were filled with coagulated serum, lymphocytes and large mononuclear cells. A few areas of caseation were present, surrounded by lymphocytes, epithelioid cells and large mononuclear phagocytic cells. The lymphoid follicles appeared to be rather small.

Bone Marrow.—A section of vertebral marrow showed many small areas of focal necrosis surrounded by lymphocytes and large mononuclear cells. There was little caseation. The remainder of the marrow showed no significant abnormalities.

Brain.—Sections taken from representative areas of the brain, spinal cord and pituitary gland showed that the leptomeninges were considerably thickened by dense infiltration with many lymphocytes, a few polymorphonuclear leukocytes and large mononuclear cells, some of which contained phagocytosed necrotic cellular debris while others were heavily vacuolated by the loss of intracellular fat. No giant cells of the Langhans type were seen. Several strands of fibrin were present throughout the exudate. Sections taken from the white nodular lesions in the region of the sylvian fissure (figs. 1 *A* and 1 *B*) showed these were made up of areas of necrosis surrounded by lymphocytes and mononuclear cells. Polymorphonuclear leukocytes were scarce in these areas. Involvement of the underlying parenchyma

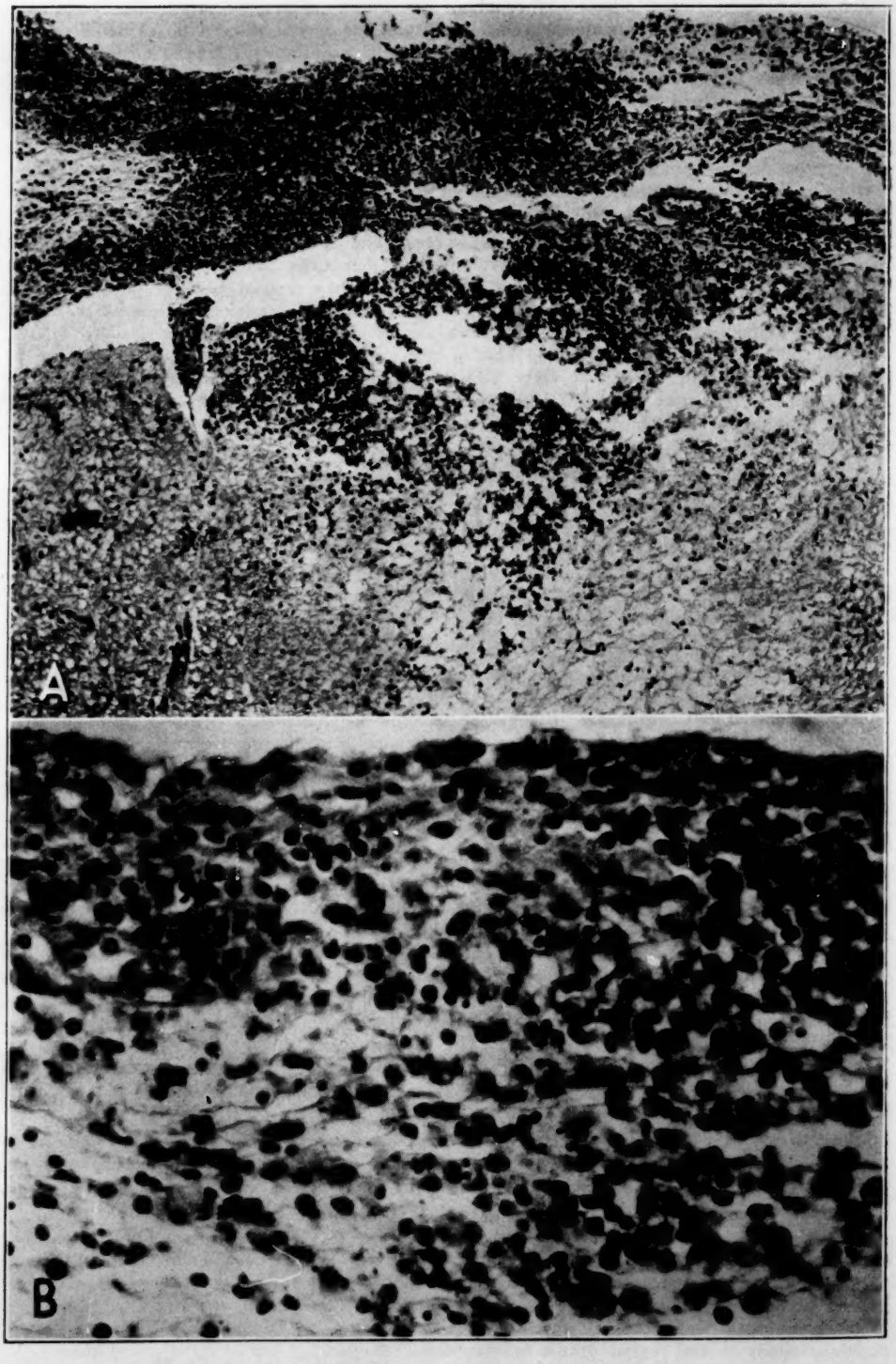

Fig. 1.—*A*, tularemic meningitis with associated encephalitis (hematoxylin and eosin; × 120). *B*, magnification of the meningeal exudate to show the types of cells involved as well as the necrosis (hematoxylin and eosin; × 525).

was evidenced by the slightly wedge-shaped areas which were heavily infiltrated with small mononuclear cells, some of which appeared to be necrotic. These areas appeared for the most part to be in close association with the meninges as they followed small blood vessels deep in the parenchyma. The ependyma, although everywhere intact, was heavily infiltrated by small round cells. A few subependymal areas of focal necrosis were seen. The choroid plexus had lost its original architecture and showed a heavy infiltration of its layers with numerous polymorphonuclear leukocytes and large mononuclear phagocytes which were filled with fat vacuoles and cellular debris. No giant cells were to be seen. The endothelial cells of the choroid plexus were greatly swollen and in a few areas appeared to be desquamated. The endothelium of all of the blood vessels was slightly swollen but otherwise appeared normal. The spinal cord showed submeningeal involvement as well as the diffuse meningitis described. The ependyma of the central canal did not show the lesions seen in the ventricular ependyma nor any other significant change.

COMMENT

In attempting to explain the pathogenesis of the meningeal involvement in this case, one may consider three possible routes of invasion. Since the child was found to have a bacteremia when she entered the hospital, the possibility exists that the infecting organism may have been introduced into the subarachnoid space at the time of the initial lumbar puncture. A second possibility is that the meningitis was secondary to the breakdown of an area of focal necrosis in the substance of the brain. Pund and Hatcher in interpreting their case considered this to be the sequence of events. However, in their case, as in ours, the lesions in the brain substance were all situated near the surface and are, we believe, more reasonably interpreted as secondary to the meningeal involvement. The remaining explanation is that the infecting organism reached the meninges directly by way of the blood stream. In a disease in which invasion of the blood stream occurs with some frequency, one would expect involvement of the meninges in a certain number of cases. To date, postmortem examination of the central nervous system has been recorded in only 10 cases. In 2 of these there was meningitis, and in 1, encephalitis.

This case is of considerable interest since it represents the first instance, to our knowledge, in which the diagnosis of tularemic meningitis was established by bacteriologic studies before death and later confirmed by postmortem examination.

SUMMARY

In a case of tularemic meningitis the diagnosis was established before death by isolation of Bact. tularense from the spinal fluid and was confirmed by necropsy.

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Progress in Pediatrics

USE OF EVAPORATED MILK WITHOUT ADDED SUGAR FOR THE FEEDING OF INFANTS

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The purpose of this paper is to point out the facts that infants fed on ordinary commercial unsweetened evaporated milk as a substitute for breast milk grow satisfactorily in every respect when no sugar or other carbohydrate is added to the daily formula, provided the milk is used in amounts sufficient to satisfy total caloric needs.

Breast feeding should be given if it is possible, since an infant thrives best when fed breast milk. Both morbidity and mortality are lower in breast-fed babies,[1] and every other evidence of growth, nutrition and development indicates the advantages of breast feeding. But it is also true that there are exceptional instances in which breast-fed babies may be inadequately nourished and such conditions as tetany, anemia and, more often, general but less specific malnutrition may occur. These conditions are related more often to the physical health of the nursing mother and to her general nutritional and economic status than to any defect in the infant. A large proportion of these inadequately breast-fed infants are found in the urban population, the babies of young, modernized mothers who are below physical standards in general and who live under complex, tense, hurried and distracting conditions.

The use of evaporated milk as a food for infants and children has increased rapidly.[2] There are many advantages to recommend its use. It is cheap, uniform in quality in various brands, readily available in every community and in every season and convenient to prepare. It is subject to control through federal and state food and drug laws. The content of fat, protein and carbohydrate is consistent. The fat is small in amount and exists in homogenized form. Evaporated milk is believed by most investigators to be more easily digested than fresh milk, possibly as the result of certain changes which take place in the protein fraction during the process of evaporation and superheating. There is also some change in the lactose fraction which gives the milk a sweeter, slightly caramelized flavor. Evaporated milk is better tolerated than fresh milk by infants who are allergic to the proteins in milk. By varying the amount of water used to dilute the evaporated milk, the formula can be made suitable for infants of various ages, and especially for infants who vomit easily, since the milk can be given in a concentration higher than that of fresh milk.

PROCEDURE

Since 1936, infants coming under my care have been fed entirely and without exception on evaporated milk whenever breast milk has not been available, and the formula has been prepared always without the addition of any form of carbohydrate. The infants have been like those usually seen in the conduct of a pediatrician's practice and observation has begun at birth with full term or premature babies and continued through the usual milk-drinking period; both well and ill infants have been included. The children were usually given evaporated cow's milk, but a few, in whom an allergy to milk was suspected, received evaporated goat's milk. Infants weighing as little as 3 pounds (1,300 Gm.) at birth received the same formula as larger ones. In feeding small, slowly growing infants and rapidly growing ones only the quantity of the formula given was varied. The reaction to this type of feeding has been so satisfactory that the method is being continued and its general use is recommended. The procedure was started while investigations were in progress to determine the cause of the increased number of stools and occasional diarrhea in newborn infants fed on evaporated milk containing various sugars and syrups. At that time it seemed that changes in the milk during its evaporation might be the cause for this condition, but there were several features which suggested that the added sugar in the formula

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1. Grulee, C. G.; Sanford, H. N., and Herron, P. H.: Breast and Artificial Feeding: Influence on Morbidity and Mortality of Twenty Thousand Infants, J. A. M. A. **103**:735 (Sept. 8) 1934.

2. Grulee, C. G.; Sanford, H. N., and Lewison, M.: Irradiated Evaporated Milk as a Food for Infants, J. Pediat. **14**:725 (June) 1939.

was the cause of the diarrhea. Subsequently, and independently of this investigation, a report by McMahon [3] indicated the value of feeding evaporated milk to the newborn infant without the addition of sugar.

The use of evaporated milk was substituted completely for breast feeding as soon as it was clear that an infant was receiving an inadequate supply of breast milk although every known procedure had been tried to improve the mother's nursing condition. No attempt was made to use both breast and bottle feeding. The amount of food and the number of feedings required in twenty-four hours were determined by the size, growth and development of the infant, and by his reactions and behavior. This amount was offered at intervals during a reasonable nursing time, and the infant was allowed to take an unspecified amount sufficient to satisfy his hunger. As the infant grew, the amount of food and the interval between feedings was changed to meet new conditions, particular attention being given to manifest behavior and reactions of the infant rather than to an age schedule or any artificial rule.

The food was prepared according to accepted principles in use generally, but since sugar was not added many details of the procedure became unnecessary and could be eliminated. The vessels for heating and mixing, utensils for stirring and pouring and much special apparatus could be done away with. The following instructions were given.

Wash and clean with soap and water the bottles required for feeding for twenty-four hours, using a brush inside; boil them in clear water and allow them to cool. When they are cool, empty them and place them upright on a table. Wipe two opposite edges of the top of a can containing evaporated milk with a ball of cotton moistened with alcohol; if necessary, clean first with soap and water. Using a clean can opener of the punch type, make a large hole on one side and a smaller one on the opposite side of the can, so that the milk may be poured directly into the feeding bottle; use a finger over the small hole to control the flow of milk. A clean boiled funnel may be used to pour the milk directly into the bottle. Empty the can (13 fluid-ounces, about 400 cc.), placing approximately the same amount in each bottle. Place sterilized caps or small balls of cotton over or in the sterile openings and put the bottles in the ice box or some other cool place.

At the feeding time add boiled or otherwise safe, fresh water to the bottle up to the desired amount, depending on the fluid requirements of the individual infant. This amount may vary from none to enough to make a full 8 ounce (240 cc.) bottle, but the total amount of milk and water should be in excess of the optimum intake at each feeding. Part or all of a second can of milk may be needed for a large, hungry infant. Since the food will be consumed immediately after it is prepared, it is frequently possible to avoid boiling the water, if the latter is considered safe for drinking for the general population of the community. Warm the bottle containing the mixture of milk and water, carefully, to body temperature; put a clean nipple in place and feed the infant whatever amount he desires. Milk left in the bottle from a feeding must always be thrown away.

RESULTS

Infants who have been fed according to this principle have shown certain characteristics which may be grouped under (*a*) growth and nutrition, (*b*) food tolerance and digestion and (*c*) nursing technic and behavioral reactions.

Growth and Nutrition.—When no breast milk was available and food prepared by this formula was used starting on the fourth day of life, the birth weight was regained more slowly than when breast milk was used—usually by the fourteenth to the eighteenth day instead of between the tenth and the fourteenth day. The recovery was steadier, however, there being a small gain each day instead of wide fluctuations. This slow recovery should be explained beforehand to an anxious mother. The even gain continued throughout the neonatal period, and by the end of the first three months the infants were well up to average in weight. No unusual changes in linear growth were observed.

The general appearance of the infants was uniformly good. The peripheral circulation was satisfactory, owing in part to vigorous exercise from hunger crying and other activity which prevented chilling and mottling, especially of the feet and hands. Insensible perspiration was sufficient, but there was no tendency to unusual sweating. The skin was smooth, uniform, faintly moist, warm and flexible. The control of body temperature seems to be more uniform in infants fed in the manner described.

The subcutaneous fat was moderate in amount, unusually firm and evenly distributed over the whole body; for this reason the infants looked thin, especially about the trunk and thighs. Mothers should be informed why babies fed this diet will not appear fat. It was interesting to

3. McMahon, H. O.: A Simplified Infant Feeding Formula: A Report of the Use of Irradiated Evaporated Milk and Water in Two Thousand and Four Cases, Wisconsin M. J. **38**:874 (Oct.) 1939.

observe the conversion of an obese baby who has been fed according to a formula calling for large amounts of sugar into a lean, muscular, active infant when the diet was corrected by substituting evaporated milk without sugar. During the period of conversion, linear growth continued while the total body weight remained stationary until all excess fat had been used.

In these infants the muscles were firm in tone, about the usual size but more apparent because of the thinner layer of fat. No roentgenographic study of the bones was made, but when adequate quantities of vitamins D and C were provided the epiphysial areas remained smooth and normal and no changes indicative of a deficiency in these vitamins were observed.

Food Tolerance and Digestion.—Food was well retained, since the infants were hungry at each meal and no forcing was necessary. Since the total amount of fluid in an individual feeding was adjusted to satisfy both hunger and thirst, the stomach was not overfilled. Regurgitation or vomiting rarely occurred unless there was some fault in nursing technic. Pylorospasm was not observed, and there was no evidence of unusual retention of food.

In most cases the abdomen remained small and the infant showed less distention and expelled less gas than is usual. Those who had distention usually showed subsequent signs of intolerance for fat even in the homogenized condition and in the small amounts present in evaporated milk.

The stools from these infants had the general appearance of those from breast-fed babies. They were uniform in color and consistency, smooth and moderate in size; defecation occurred two to four times daily, while it occurs more frequently in colicky babies. It is particularly important to emphasize that infants fed on this principle did not become constipated. This observation may be the most significant of all, since one of the reasons for adding carbohydrate to a milk formula has been its laxative effect. Whether this laxative effect is due to changes in the bacterial flora of the intestinal tract, changes in the acid-base relation in the intestinal contents with fermentation of the additional sugar, or the action of secondary substances contained in syrups and special preparations of sugar is not clear. The addition of a laxative substance may be necessary when infants are fed other milks,[4] but it is not needed when evaporated milk is used.

When ascorbic acid was used instead of fresh orange juice during the first three months, further improvement was observed in digestion with still greater freedom from colic and with normal intestinal activity. It may be that the high content of sugar in orange juice was the factor responsible for the less favorable reactions when it was used, or there may have been intolerance to orange.

Nursing Technic and Behavioral Reactions.—Infants given this diet seemed hungry before feedings and after the proper emptying time of the stomach, usually three to four hours. They awakened spontaneously, cried lustily from hunger, nursed eagerly until satisfied and then slept better than when fed according to other formulas.

The infants were unusually alert and responsive, particularly during the early weeks and even in the first two weeks after birth.

Satisfaction of hunger as judged by the child's activities sometimes required seven or even eight feedings in twenty-four hours during the first six to ten weeks. In spite of statements to the contrary, many infants were most comfortable on a schedule of frequent feedings. This was particularly true for active, hyperkinetic infants.

The infants learned good eating habits early and easily; hence secondary foods could be added as soon as an infant showed tonguing and chewing movements. By careful selection of waters and purées of green and yellow vegetables, fresh fruit juices, given plain or preferably in gelatin preparations, and meat juice and pulp for addition to the diet, it is possible to conform to the same plan of restricting the intake of sugar, and thereby to maintain the same general characteristics of growth seen in the earlier period. These foods contain vegetable starches in amounts sufficient to satisfy the growing hunger and the increasing caloric needs of the infant.

COMMENT

Evaporated milk without added sugar given in the manner described is proposed as a suitable food for all normal infants and small children during the important period during which milk constitutes most of the diet. It is proposed, also, that this formula can be used for infants with gastrointestinal disturbances and with parenteral infections and diseases. By adjusting the content of water in the formula, the interval between feedings and the total amount of milk fed, an adequate supply of food can be maintained. Additional salt can be used when needed, and either lactic or hydrochloric acid can be added when it is necessary to replace either acid or chloride lost through vomiting. Additional fluid to which the acid can be added in a palatable form can be given between feedings, or fluids and amino acids can be administered parenterally according to indications.

4. Holt, L. E., and McIntosh, R.: Holt's Diseases of Infancy and Childhood, ed. 11, New York, D. Appleton-Century Company, Inc., 1940, p. 148.

There were variations and exceptions in individual infants among those studied; however, none of these were great enough to justify changing the type of milk and the plan of feeding. In these cases much patience and many adjustments were necessary until a satisfactory routine was established. It is proposed that if an individual infant fails to respond properly to this type of feeding some adjustment be made in the technic of feeding or search be made for some underlying defect in the infant's digestion of the fat or protein of milk.

There are several advantages of this type of feeding aside from the characteristics which have been described. The preparation of the formula is simple. Adjustments to new levels must continue to be made under the direction of a physician; the formula is not turned over to the mother for her own interpretation and application. The emphasis is placed on observing the growth, nutrition and development of the infant, and the corresponding changes are based on these factors rather than on age, custom or a preestablished schedule. This requires pediatric experience and training. The problems associated with the use of sugar in the formula are avoided. The innumerable sugars and other carbohydrates for the feeding of infants are bewildering even to the physician. Fortunately, because of controlled advertising, the claims for these sugars do not often reach the mother or the situation would be worse still. One further advantage is the availability of the mineral constituents of milk, particularly of calcium and phosphate, which are involved in protein metabolism. The relationships of the vitamins to protein and carbohydrate metabolism are being widely studied at the present time. It is now established that the nutritional requirements for certain elements of the vitamin B complex are related directly and proportionately to the utilization of carbohydrate. The lower intake of carbohydrate with this diet thus spares the available amounts of these vitamins in the milk.

This type of feeding may be considered high in protein though the values are only relative. The infant is supplied with a higher quantity of protein because the content of carbohydrates in a given amount of food is reduced. This shift in value should be an advantage, since there is ample evidence that the requirements for growth and nutrition include adequate supplies of protein and that the body will utilize larger amounts of protein than was previously supposed. There is also suggestive evidence that an adequate supply of proteins, particularly when such proteins are complete in essential amino acids, may serve as a stimulus to optimum growth. During the period of extremely rapid growth in early infancy these factors are unusually important.

The inclusion of milk in the diet produces changes in the enzymatic activity and the growth of bacteria in the intestine, depending, ordinarily, on the type of milk used. The protein of milk, with its high content of calcium caseinate, ordinarily produces alkaline stools the color of which depends on the amount and state of digestion of the residual fat, while the protein of meat produces acidified intestinal contents due to the proteolytic activity of enzymes and organisms.

In the diet described, carbohydrate requirements are met adequately by the content of lactose in cow's milk, by the amount of dextrose which can be formed during protein metabolism and by further use of available fats to satisfy caloric needs rather than for storage. The disadvantage of a diet high in sugar for older infants and children is generally recognized. The harmful effects of a diet high in sugars and inert carbohydrates on growth, hemopoiesis, the metabolism of bone and of teeth, the control of body weight and resistance to infection have been discussed frequently. As age increases the harmful effects are still more easily recognized.

This type of feeding does not represent an attempt to streamline the formula or the routine for feeding infants in any degree. It is used, also, independently of any factor which determines the use of secondary foods in feeding infants, such as the cereals, vegetables, meats and fruits necessary for older infants.

SUMMARY

When a sufficient supply of breast milk is not available, infants may be fed by choice, and will do well, with various dilutions of irradiated, homogenized, unsweetened evaporated cows' milk. Criteria such as gain in weight, rate of growth, general nutritional status, satisfactory sleeping habits, normal stool formation and absence of indigestion indicate that such feeding is adequate and satisfactory.

Evaporated milk as a food for infants may be used with increased advantages if no sugars or other carbohydrate is added to those present naturally in milk. There is evidence of more uniform and satisfactory nutrition and growth during the period of infancy with a feeding of this type.

It is suggested that added sugar in the diet of infants and small children may produce the same changes in growth and nutrition that carbohydrates produce in older children and adults.

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Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

Bactericidal Action of Ultraviolet Radiation on Air-Borne Organisms. Harvey C. Rentschler and Rudolph Nagy, J. Bact. **44**:85 (July) 1942.

By means of specially devised apparatus the authors were able to find that sensitivity to ultraviolet radiation of air-borne bacteria and of similar organisms on the surface of agar is the same. They describe experiments which show that bacteria may be injured by heat, Grenz rays or roentgen rays so that the surviving organisms are less resistant to ultraviolet radiation. According to them this is incompatible with the "single photon hit" theory. They state that not all the bacteria in a pure strain of a culture are identical and the term, k, in the exponential equation generally used for expressing the survival ratio for different exposures to ultraviolet radiation is not a constant, as is commonly assumed. Furthermore, the air centrifuge, as used in determining the bacterial contamination of air moving through a duct at low humidity, is selective in taking the bacteria from the air. This may explain the reason for the general statement that air-borne bacteria at low humidity are more vulnerable to ultraviolet radiation than when on the surface of agar and that at low relative humidity the bactericidal action is greater than at high humidity. The paper should be consulted for a complete description of the apparatus employed and the details of the interpretation of the results obtained.

Stoesser, Minneapolis.

Observations on Reversibility of the Quellung Reaction and Relation Between the Quellung Reaction and Bile Solubility. Alice H. Kempf and W. J. Nungester, J. Infect. Dis. **71**:50 (July-Aug.) 1942.

Kempf and Nungester present this summary:

The quellung reaction of pneumococci with immune serum has been demonstrated to be reversible. The amounts of polysaccharide necessary to prevent or to reverse this phenomenon when a given quantity of antiserum is used have been determined. In pneumococci in which the quellung reaction has occurred, bile solubility, as determined by clearing of the suspension and by the numbers of viable bacteria, has been shown to be greatly delayed.

Lysis occurred in the presence of sufficient polysaccharide to prevent the reaction, and the turbidity was only slightly greater than that in a tube containing only pneumococci and bile. This was likewise true of a suspension in which the swelling of the capsules had disappeared after the addition of specific polysaccharide.

The quellung reaction was also reversed by repeated washing of the organisms with water.

Toomey, Cleveland.

The Serological and Biological Classification of Hemolytic and Nonhemolytic Streptococci from Human Sources. Lowell A. Rantz, J. Infect. Dis. **71**:61 (July-Aug.) 1942.

Studies have been made of 392 strains of hemolytic and nonhemolytic streptococci isolated from human clinical materials obtained from other sources than the respiratory tract.

Biologic and serologic classification was undertaken by the methods of Sherman and Lancefield.

Of all strains 81.9 per cent could be assigned to a Lancefield group.

The clinical source, biologic characteristics, type of hemolysin formation and colonial form of the members of each group are presented and discussed.

Biologic methods were most valuable in the differentiation of members of group D.

Toomey, Cleveland

The Effect of Temperature upon the Growth and Survival of Myxoma, Herpes and Vaccinia Viruses in Tissue Culture. Randall L. Thompson and Margaret S. Coates, J. Infect. Dis. **71**:83 (July-Aug.) 1942.

Minced chick embryonic tissue suspended in a mixture of serum and Tyrode's solution and dispensed in large test tubes was found to be a convenient medium for the study of growth and survival of the viruses of myxoma, of herpes and of vaccinia at different temperatures.

The maximum growth of each virus occurred between 34 and 35 C. in cultures incubated for four days. Herpes virus was not demonstrated in cultures incubated at 40.2 C.; myxoma virus did not survive at 42.2 C. The New York Board of Health strain and the Noguchi strain of vaccinia virus remained viable in cultures incubated at 45.1 C., but the second revived strain failed to survive for four days. TOOMEY, Cleveland. [AUTHORS' SUMMARY]

THE DEATH OF TUBERCLE BACILLI SUBJECTED TO OXYGEN DEPRIVATION IN THE PRESENCE OF MOISTURE AND OF WARMTH. TRUMAN SQUIRE POTTER, J. Infect. Dis. **71**:220 (Nov.-Dec.) 1942.

When severely restricted in supply of oxygen in the presence of moisture and of warmth, human, bovine and avian tubercle bacilli slowly lose their capacity for subsequent growth, both in culture and in tissues of animals. TOOMEY, Cleveland. [AUTHOR'S SUMMARY]

BETA HEMOLYTIC STREPTOCOCCI ISOLATED FROM PUBLIC ROOM FLOORS. WILLIAM G. WALTER and G. J. HUCKER, J. Infect. Dis. **71**:237 (Nov.-Dec.) 1942.

Beta hemolytic streptococci were isolated from the sweepings from the floor in 22 of the 37 rooms investigated in six schools, a boys' dormitory, a theater and a hotel. An enrichment medium containing blood and potassium tellurite was used to enhance the growth of the hemolytic streptococci present in the dust.

There was a seasonal variation in the ease with which these organisms could be isolated, cold weather favoring their recovery. By physiologic and serologic tests performed on 17 representative cultures 7 were classified in Lancefield's group A, 2 in group B, 1 in group C and the remaining 7 possibly in group G. Thirty-nine additional cultures might be grouped similarly on the basis of physiologic studies. TOOMEY, Cleveland. [AUTHORS' SUMMARY]

FACTORS IN THE PRESERVATION OF THE DISTEMPER VIRUS. HEINZ A. SIEDENTOPF and ROBERT G. GREEN, J. Infect. Dis. **71**:253 (Nov.-Dec.) 1942.

Homogenized, modified distemper virus taken from a ferret, diluted in 25 per cent sterile normal horse serum and stored at —24 C. retains most of its virulence for ferrets longer than 693 days. The diluted virus does not lose its infectivity for ferrets on exposure to sunlight for seven and one-half hours. Modified distemper virus dried from the sample in a frozen state in vacuum, sealed in the original vacuum and stored at 7 C. remains infectious for ferrets after 430 days of storage. Quick freezing is not necessary for the preservation of this virus.

Dry air and commercial nitrogen that contains 0.5 per cent of oxygen have a deleterious effect on the dried virus. Drying the virus from the sample in a frozen state is essential to preservation of its virulence. Modified distemper virus sealed in oxygen-free dry nitrogen retains its infectious property for at least 365 days of storage at 7 C.

TOOMEY, Cleveland. [AUTHORS' SUMMARY]

THE ANTIGENIC STRUCTURE OF THE BACTERIA INCRIMINATED IN FOUR UNRELATED OUTBREAKS OF FOOD INFECTION. M. W. HENNING, South African M. J. **16**:253 (July 11) 1942.

Details of the four outbreaks were given earlier (*South African M. J.* **16**:125 [March 28] 1942). Two were caused by Salmonella braenderup, one by Salmonella enteritidis and one by the IV-variant of Salmonella typhi murium. Although the two strains of S. braenderup were serologically identical, they showed minor biochemical differences.

GONCE, Madison, Wis.

Metabolism; Infant Feeding; Milk and Other Foods

STUDIES CONCERNING MECHANISM CONTROLLING INITIATION OF LACTATION AT PARTURITION. JOSEPH MEITES and C. W. TURNER, Endocrinology **31**:340 (Sept.) 1942.

Results of experiments on rabbits indicate that the act of nursing plays a role in the initiation of milk secretion to the extent that maximum lactation and maximum lactogen in the pituitary gland cannot be obtained without it. Furthermore, in the absence of the suckling stimulus after parturition, the lactogen content of the pituitary declines rapidly and secretion of milk soon ceases. JACOBSON, Buffalo.

THE EFFECTIVENESS OF LINOLEIC, ARACHIDONIC, AND LINOLENIC ACIDS IN REPRODUCTION AND LACTATION. F. W. QUACKENBUSH, F. A. KUMMEROW and H. STEENBOCK, J. Nutrition **24**:213 (Sept.) 1942.

In view of their results, the authors recommend that in studies on reproduction and lactation rats should receive at least 100 mg. daily of the essential fatty acids or their equivalent in the form of a natural oil. Ethyl linoleate and ethyl arachidonate prevented or cured the dermal symptoms completely and enabled the mother to produce normal young. Ethyl linolenate was ineffective. The requirements for these acids were about twice as high for reproduction as for cure of dermal lesions in fat deficiency.

FREDEEN, Kansas City, Mo.

THE SULFUR METABOLISM OF CHILDREN. ELIOT F. BEACH, D. MAXWELL TEAGE, OLIVE D. HOFFMAN, BERTHA MUNKS, FRANCES C. HUMMEL, HAROLD H. WILLIAMS and ICIE G. MACY, J. Nutrition **24**:257 (Sept.) 1942.

Eliot F. Beach and his co-workers in their study of the metabolism of 8 normal children 8 to 12 years of age, over a forty-five day period studied the excretion and retention of sulfur and the urinary sulfur partition in relation to nitrogen metabolism. The urinary elimination represented 77 per cent of the sulfur intake and 82.8 per cent of the nitrogen intake. Inorganic sulfur composed 84 per cent of the urinary excretion of that element. The average daily excretion of ethereal sulfur was 48 mg, and of neutral sulfur 70 mg. With increasing age there was generally a decreasing laxation rate (bowel movements per day) and an increased urinary output of ethereal sulfur. Under the conditions of this experiment, there was a definite relationship between output of neutral sulfur and recumbent body length, while only remote relationship was noted between output of neutral sulfur and age, body weight and surface area. The average nitrogen to sulfur ratios for intake, feces and urine were 13.4, 10.5 and 14.4, respectively. The nitrogen to sulfur ratio of the retentions averaged 8.8; however, if this was corrected to include losses through the skin, the ratio was nearer 15, which has been indicated as the ratio for the entire body by analyses of muscle tissue.

FREDEEN, Kansas City, Mo.

THE EFFECT OF PANTOTHENIC ACID DEFICIENCY ON THE BLOOD LIPOIDS OF THE DOG. J. V. SCUDI and MARGARET HAMLIN, J. Nutrition **24**:273 (Sept.) 1942.

Scudi and Hamlin found that dogs maintained on pantothenic acid-deficient diets had lowered blood levels of cholesterol, cholesterol ester, lipid phosphorus and total lipids. The lipid levels of the blood were rapidy increased after the administration of the vitamin. Pantothenic acid-deficient dogs acquired extremely fatty livers. Dogs receiving whole dried liver in addition to the pantothenic acid showed minimal hepatic damage.

FREDEEN, Kansas City, Mo.

THE INTERRELATIONSHIP OF CALCIUM, PHOSPHORUS AND NITROGEN IN THE METABOLISM OF PRE-SCHOOL CHILDREN. JEAN E. HAWKS, MERLE M. BRAY, MARJORIE OLSON WILDE and MARIE DYE, J. Nutrition **24**:283 (Sept.) 1942.

In their studies with 5 preschool children over fifteen to twenty-four day periods on diets containing 3 Gm. and then 4 Gm. of protein per kilogram of body weight, the authors found that the higher protein diet had no effect on absorption or retention of calcium. However, there was a decreased absorption of phosphorus but a better utilization of the amount available. An increase in both absorption and retention of nitrogen was noted on the higher protein diet. Gains in weight were greater on the higher protein diet; the authors suggested that muscle and other soft tissue accounted for the greater proportion of the increased weight since there was decided increase in nitrogen retention and significant changes in retention ratios for the following elements: calcium/phosphorus; sodium/calcium; nitrogen; total phosphorus, and nitrogen/nonosseous phosphorus.

FREDEEN, Kansas City, Mo.

THE EFFECT OF GLUCOSE AND SUCROSE ON THE RESPIRATORY QUOTIENT AND MUSCULAR EFFICIENCY OF EXERCISE. MARGARET WRIGHTINGTON, J. Nutrition **24**:307 (Oct.) 1942.

Wrightington found that the respiratory quotient of persons at rest six to eight hours after the last meal with no dietary control varied from 0.69 to 1. When the supply of carbohydrate was in excess of that of fat, the latter was formed from carbohydrates; this occurred at respiratory quotients above 0.90. The reverse occurred when the quotient was below 0.80.

Sucrose, probably owing to the conversion of its fructose component to fat, raised the rest respiratory quotient higher than did dextrose (d-glucose). Her data showed that more dextrose than sucrose was metabolized during work. However, no change in muscular efficiency occurred after the ingestion of either sugar.

FREDEEN, Kansas City, Mo.

CALCIUM, PHOSPHORUS AND NITROGEN METABOLISM OF YOUNG COLLEGE WOMEN. H. MCKAY, M. B. PATTON, M. A. OHLSON, M. S. PITTMAN, R. M. LEVERTON, A. G. MARSH, G. STEARNS and G. COX, J. Nutrition **24**:367 (Oct.) 1942.

McKay and associates concluded that the calcium allowance of 1 Gm., as recommended by the Committee on Food and Nutrition of the National Research Council, for girls of 16 to 20 years might likewise be recommended for the group 17 to 24 years old, women of college age. Figures of regression of balance on intake showed that mean daily intakes of 0.8 Gm. of calcium, 1 Gm. of phosphorus and 9 Gm. of nitrogen, respectively, are required for equilibrium.

FREDEEN, Kansas City, Mo.

ARTIFICIAL FEEDING OF HEALTHY INFANTS IN HOSPITALS. A. ARIZTIA and F. EGGERS, Rev. chilena de pediat. **13**:73 (Feb.-March) 1942.

The authors contrast results in the feeding of infants a few decades ago with those in the feeding of the same type of hospital population today. The infant mortality of those periods often reached figures as high as 60 per cent. Today it is less than 10 per cent in spite of the fact that a much smaller number of infants in hospitals today receive breast milk and that such infants are fed almost exclusively on other food, such as milk of the ass or of the cow or one of the now popular forms of processed milk.

The specter of the old picture of "hospitalism" has vanished.

The improved conditions obtained with almost exclusive artificial feeding the authors do not ascribe to a superiority of present day artificial feeding over breast milk feeding but rather to better knowledge of sanitary factors in care of milk, care of the infant, prevention of cross infection and regulation of environmental temperature of the infant. It is a combination of all these factors which has brought about the better results of today as compared with experiences of the past.

The authors call attention to the importance of providing for the minimum feeding requirements of the infant when diluted milks or partially skimmed milks are used. They consider this a necessary factor in maintaining immunity against the common prevailing infections.

SCHLUTZ, Chicago.

MEDICAL, SOCIAL AND ECONOMIC STUDY OF THE FEEDING OF WELL INFANTS IN THE ORGANIZATION FOR THE PROTECTION OF MATERNAL WELFARE IN CHILE. G. MORALES BELTRAM and W. B. ESPINOZA, Rev. chilena de pediat. **13**:103 (Feb.-March) 1942.

The authors conclude that the proper feeding of healthy infants is, without doubt, basically fundamental in the program of infant welfare. The agencies which now are functioning for the feeding of healthy infants and which are scientifically managed are consultation stations organized by the office of the Works Security Program and the milk stations of the city of Santiago, under the patronage of the National Child Welfare Program. It is necessary to provide services both in urban and in rural areas for some 90,000 infants, who, according to the authors' reports, need primarily adequate feeding in order that they may subsist.

In the opinion of the authors, the best system for this phase of infants' care is that of the milk station, the program and regimen of which should be extended throughout the entire country. Wherever possible the Works Security Program must also function in this organization. In Santiago and in the provinces milk stations should be established in sufficient number to take care of all the needy infants of the country and should be provided preferably with fresh milk. If this cannot be obtained, condensed preparations may be used.

In order that the milk stations may render the best possible service, it is necessary also to organize auxiliary aid by addition of food for the rest of the family, so that preschool children can have breakfast and school lunches and so that it will not be necessary to parcel the milk needed for the baby out to the rest of the family.

Control of the feeding in the homes is difficult and depends fundamentally on educational measures and persuasion by the medical personnel, the social service visitors and the health nurses.

To have general application of all the technics which operate for the protection of the infant, it is necessary to make available to as large a number of infants as possible the

benefits provided by law and at the same time to procure personnel at the respective stations and to provide economic conditions which will enable proper and efficient attention to be given to the problem of child welfare.

It is not necessary to establish a standardized system of feeding, because it has been found that various feeding programs, such as use of fresh cow's milk, dried milk or condensed milk, work equally well if properly carried out.

The authors state that the amount of milk provided for the infant should not be particularly reduced when he reaches the age at which he can take additional solid foods, such as purées, vegetables and fruits, and that his rate of gain is higher and more satisfactory if his adequate intake of milk is retained.

The authors express the opinion that a permanent commission for the supervision of feeding of infants is indispensable in the program. This commission should determine technics of normal feeding at the various periods of life and in the various areas of the country

SCHLUTZ, Chicago.

ARTIFICIAL FEEDING OF HEALTHY INFANTS. J. A. BAUZA, Rev. chilena de pediat. **13**:109 (Feb.-March) 1942.

In the feeding of healthy infants in the welfare stations in Montevideo, Uruguay, the author has been more successful with acid milks than with simple diluted cow's milk and with powdered milk preparations than with fresh cow's milk.

Buttermilk in the form of powder, diluted so that the solution contains 10 per cent of solids, with 1.5 per cent of fat and 1.5 per cent of sugar added, usually constitutes the initial feeding.

Sometimes the butter-flour mixture of Czerny is added to the buttermilk.

The authors stress the importance of giving vitamins C and D at an early stage of the feeding program.

SCHLUTZ, Chicago.

ECONOMIC AND SOCIAL ASPECTS OF ARTIFICIAL FEEDING IN THE PROGRAM OF INFANT WELFARE PROTECTION IN BUENOS AIRES. M. H. BORTAGARAY, Rev. chilena de pediat. **13**:121 (Feb.-March) 1942.

In the city of Buenos Aires, Argentina, fresh cow's milk is mostly used for artificial feeding of infants in the welfare stations, and it is seldom necessary to resort to the use of condensed or dried milks. Great care is used in the supervision of the feeding in the home and in the kitchens in connection with the established dispensaries. The general educational influences which can be brought to bear on the poorer and more ignorant classes through such measures have, in the opinion of the author, diminished many of the dangerous factors which menace infants.

Artificial feeding of infants in the city of Buenos Aires has so far not presented serious economic or social aspects. The organization now existing can be improved in minor details. The author contends that intensive measures of propaganda should be continually undertaken, so that it will not be necessary for any infant or other person to be without adequate help or advice.

SCHLUTZ, Chicago.

VITAMINS AND ARTIFICIAL FEEDING. J. P. GARRAHAN, Rev. chilena de pediat. **13**:133 (Feb.-March) 1942.

The author believes that in creating optimal conditions for the nutrition of the healthy infant one cannot exclude the necessity of giving special vitamins. In the majority of cases it is necessary to provide supplements of vitamins A and C, and often it is necessary to add thiamine or the vitamin B complex. The average physician must be better acquainted with the needs of the artificially fed infant in this respect than he is at present and must learn to recognize more readily than he does now the occasion when such need arises.

The author points out the necessity of adding vitamin D to the food and of not depending too much on solar irradiation.

SCHLUTZ, Chicago.

Vitamins; Avitaminoses

FACTORS INFLUENCING THE LEVEL OF VITAMIN A IN THE BLOOD OF RATS. HUGH W. JOSEPHS, Bull. Johns Hopkins Hosp. **71**:253 (Nov.) 1942.

The level of vitamin A in the serum is constant under wide variation of intake. The ingestion of large amounts of vitamin A raises the level in the serum, especially if the tissues have good stores.

Rats on a deficient diet reach depletion by the twentieth day, but symptoms do not appear until one week later. It is thought that metabolic changes precede the anatomic changes.

LYTTLE, New York.

STUDIES IN VITAMIN A: INFLUENCE OF VITAMIN A ON SERUM LIPIDS OF NORMAL AND DEFICIENT RATS. HUGH W. JOSEPHS, Bull. Johns Hopkins Hosp. **71**:265 (Nov.) 1942.

Vitamin A deficiency in rats is associated with a fall in serum lipid levels. When rats rendered deficient were given excessive amounts of vitamin A, the rise in serum lipid and vitamin A levels was more pronounced and lasted longer than in the normal animals.

The experiments indicate that the fall in serum lipids was due specifically to the vitamin A deficiency and not to the nutritional state of the animal, and the subsequent rise in lipids is attributed to a specific effect of vitamin A.

LYTTLE, New York.

NICOTINIC ACID IN FOODS. ROBERT W. MCVICAR and GEORGE H. BERRYMAN, J. Nutrition **24**:235 (Sept.) 1942.

From a résumé of the literature McVicar and Berryman present a table showing the nicotinic acid in various foods.

FREDEEN, Kansas City, Mo.

STUDIES ON THE TOXICITY AND PHARMACOLOGY OF RIBOFLAVIN. KLAUS UNNA and JOSEPH G. GRESLIN, J. Pharmacol. & Exper. Therap. **76**:75, 1942.

Riboflavin was not toxic to rats and dogs when given by mouth in doses greatly exceeding those given to human beings, even when administered over a period of four months. This is probably due to its low solubility. When it was given by intraperitoneal route to rats in much larger doses than those given to human beings it was fatal because of the damage to the kidneys.

PILCHER, Cleveland.

EVALUATION OF NICOTINIC ACID NUTRITION BY STUDIES OF URINARY EXCRETION. GRACE A. GOLDSMITH, Proc. Soc. Exper. Biol. & Med. **51**:42 (Oct.) 1942.

The urinary excretion of nicotinic acid and its derivatives as determined by the method of Perlzweig, Levy and Sarett, of 34 human subjects (6 normal persons, 18 hospital patients without signs of deficiency disease and 10 patients with clinical findings indicative of deficiency of one or more members of the vitamin B complex) revealed no essential differences to be present. Trigonelline, the main excretion product of nicotinic acid, was found to be lowest in the patients with pellagra, ariboflavinosis and thiamine deficiency. Sixteen persons were given 300 mg. of nicotinic acid amide orally, and the urinary excretion of trigonelline was again studied. It was found that when the total output in a control twenty-four hour period was subtracted from the extra excretion after the nicotinic acid was given, the retention of nicotinic acid amide appeared to be closely related to the degree of dietary deficiency.

HANSEN, Minneapolis.

INVESTIGATION OF THE EFFECT OF ADMINISTRATION OF VITAMIN B_1 UPON GASTRIC SECRETION AND THE MOTOR ACTIVITIES OF THE STOMACH: A PRELIMINARY REPORT. B. WOOD, B. SPLATT and I. MAXWELL, M. J. Australia **2**:263 (Sept. 19) 1942.

The gastric content of free hydrochloric acid, total acidity, bile, starch and mucus of 36 patients having achlorhydria or hypochlorhydria and of 4 healthy students was not influenced by the daily intramuscular injection of 1,000 to 3,000 U. S. P. units of vitamin B_1 for ten consecutive days. Such treatment did hasten the emptying time of the stomach of subjects whose gastric emptying time was habitually much longer than normal but did not influence the rate of evacuation of the stomach of subjects whose gastric emptying time was normal or excessively rapid.

GONCE, Madison, Wis.

Hygiene; Growth and Nutrition; Public Health

INFANT MORTALITY IN RURAL AND URBAN AREAS. HERBERT J. SOMMERS, Pub. Health Rep. **57**:1494 (Oct. 2) 1942.

For the United States as a whole the lowest infant mortality rate is found in cities, reflecting superior medical, public health and educational facilities. The city rate, 41.1 per thousand live births, was 11 per cent lower than the rural rate, 46.1 per thousand. Towns provided the least favorable opportunity for infant survival, having apparently sacrificed the

healthful environment of the rural area without having attained the superior facilities of the city. The town rate of 50.1 per thousand live births was 9 per cent higher than the rural rate.

SANFORD, Chicago.

RADIANT HEAT AND COMFORT. LEONARD HILL, Brit. J. Phys. Med. **5**:128 (Sept.-Oct.) 1942.

Discomfort felt in ill ventilated rooms is not due to chemical impurity of the air, because, as the author states, even in crowded rooms without ventilation the carbon dioxide content never rises nor does the oxygen content fall in amounts which have any physiologic significance. The author believes the discomfort is due primarily to "heat stagnation" and to body smells. He describes experimental evidence to substantiate the claim that movement of air alone will relieve discomfort in a small crowded chamber.

He has devised a thermometer, called the "Kata" thermometer, which by measuring the cooling and evaporating power on a surface at body temperature, shows the effect of moving air. On an empiric scale it registers satisfactory or unsatisfactory conditions.

From some experimental evidence he argues that radiant heat is the most comfortable and healthful form of heat for homes.

From his point of view, the open fire place, such as is used so much in England, is quite satisfactory.

HARTMAN, Portsmouth, Va.

PHYSICALLY HANDICAPPED PERSONS AND EMPLOYMENT. DONALD C. NORRIS, Brit. J. Phys. Med. **5**:130 (Sept.-Oct.) 1942.

This is a timely and interesting article showing that the physically handicapped group has a considerable capacity for contributing to the war effort. However, it is emphasized that the medical officer who advises about such employment should be familiar with the physiologic and anatomic requirements of industry and with the potentialities and limitations attached to the training and placing of disabled workers. Statistics from the Ford Motor Company and the Western Electric Company in the United States are discussed.

HARTMAN, Portsmouth, Va.

CERTIFICATION OF DEATH IN INFANCY. F. J. W. MILLER, Lancet **2**:269 (Sept. 5) 1942.

During 1939 an investigation into the causes of deaths of infants was carried out in Newcastle-on-Tyne. The essential feature was a personal inquiry by one of two investigators, possessing a knowledge of and experience in modern clinical pediatrics, into the fatal illness and the circumstances of the death of every infant under the age of 12 months.

After considering each death certificate in the light of all the available information and making allowances for mere differences in terminology, the author estimated that at least a third of the certificates gave an inaccurate or inadequate description of the cause of death.

After evaluation of all the information there was still a large group of deaths—41 (15 per cent) out of 272—as to the cause of which the investigators were unable to express an opinion. Thirty-three of the 41 infants had died in the home.

Among the causes of inaccuracies and errors are listed: (1) difficulty in diagnosing disease in infancy; (2) inadequacy of training in pediatrics, and (3) failure of the family to call medical aid.

The author suggests revision of the classification of causes of death by a committee of clinical pediatricians and consideration of a special form of death certificate for infants.

In addition, consideration should be given to the provision of a mechanism which would enable a physician, in cases which do not require notification of the coroner, to indicate that he does not know the cause of death, so that he can perform an autopsy before giving a final certificate.

LANGMANN, New York.

NECESSITY OF INTRODUCING THE TEACHING OF FAMILY PEDAGOGY INTO THE HIGHER GRADES OF PRIMARY SCHOOLS, INTO SECONDARY SCHOOLS, INTO NORMAL SCHOOLS FOR WOMEN AND INTO MATERNITY SCHOOLS. LUIS FELIPE GONZÁLEZ, Bol. Inst. internac. am. de protec. a la infancia **16**:185 (Oct.) 1942.

Before the Eighth Pan American Child Congress the author recommended: (1) that a knowledge of family pedagogy by parents should be considered necessary for the best fulfilment of the preschool education of their children; (2) that the International Institute for the Protection of Childhood, with headquarters in Montevideo, making use of the sources at present available for the development of this scientific activity, should promote competitions aiming to prepare the best books about family pedagogy; (3) that the teaching of family pedagogy should be included as a compulsory subject in higher grades of primary schools, in

high schools, in normal schools for women as well as in maternal schools, and (4) that the different organizations for child welfare work should carry out an intense propaganda in behalf of family pedagogy and establish clinics for this new scientific activity.

[From the Editor's Summary]

The Extradition of Minors: Means for Its Development and Revision of Its Present Idea from the Point of View of the Right of Guardianship of Minors. Luis Felipe González, Bol. Inst. internac. am. de protect. a la infancia **16**:190 (Oct.) 1942.

The author presented to the Eighth Pan American Child Congress the following recommendations:

I. That countries should lend mutual aid for the return of minors to their native country when for one reason or another they have abandoned it and are still under paternal authority.

II. That when it has been ascertained that a minor has left his own country, the means should be given for his restitution to his paternal home.

III. That in the immediate handling of the case the authorities concerned should be advised by the most rapid means of communication (telegram, radiogram, etc.) of the disappearance of the minor, and the documents of communication be sufficient proof before the competent authorities of the other country.

IV. That the minor, after authentic demand for his return has been received from the country of origin, be returned by the quickest way to his country and be placed once more in his home.

V. If the parents are unable to pay for the expenses occasioned, these must be borne by the state or by a child welfare agency; but if the economic position of the parents allows them to bear the expenses, they would be obliged to do so.

VI. From the point of view of international law with respect to minors, a revision of the idea of extradition must be made, substituting for it the idea of restitution. Thus instead of being considered within the province of penal law it would be considered within that of law for the guardianship of minors.

[From the Editor's Summary]

Acute Contagious Diseases

Sulfathiazole in the Treatment of Measles and Its Complications. Harry Gibel and Abraham M. Litvak, J. Pediat. **21**:315 (Sept.) 1942.

Although sulfathiazole had no effect on the duration of the primary pyrexia of measles and did not reduce the duration of complications such as purulent otitis media and acute bronchitis, its effect on bronchopneumonia complicating measles was highly satisfactory and resulted in a considerable lowering of the mortality rate. Only 1 death in 47 cases of measles complicated with bronchopneumonia occurred.

Stettenbenz, Buffalo, N. Y.

The Early Treatment of Poliomyelitis. John A. Toomey, J. Pediat. **21**:353 (Sept.) 1942.

In this comprehensive paper, Toomey discusses treatment of early acute poliomyelitis in all its phases.

Toomey points out that as early as 1912 Henry O. Feiss, an orthopedic surgeon, questioned the practice of immobilization by casts and splints, believing that the resultant disease of the muscles was opposed to physiologic indications. For the last twenty years Toomey has used a method of therapy in which no fixed splints or casts were applied and very early in the disease initiated active and passive massage, application of heat, hydrotherapy, electrical stimulation and reeducation of the muscles. He believes his results (early) to have been as good as those reported from use of the Kenny treatment. The main objective and principle is to keep the muscles in good tone and condition until the edema of the cord subsides (usually three weeks). Then it must be determined whether there are some nerve connections left. If there are, reeducation of the muscles supplied by these nerves is then attempted.

Toomey takes issue with Kenny that the main damage and paresis are due to muscle spasm. He recognizes that spasm or stiffness of the muscles is present and must be treated; however, this does not explain muscular paresis occurring without any evidence of spasm. Also many patients soon recover from spasm without treatment, but paresis remains. The concept of poliomyelitis as a disease of the central nervous system with destruction of the cells of the anterior horn and resultant paresis cannot be overlooked. Therefore, treatment of the muscles should be undertaken, not so much because of spasm of opposing muscle groups, but because if not treated the few remaining fibers supplied by intact axons from the cord will undergo degeneration if completely immobilized. Kenny also contends that muscular incoordination is

present. Toomey believes that this is more a lack of muscle balance than incoordination of movements such as are seen typically in cerebral spastic conditions. Mental alienation is another term used by Kenny, meaning that a patient loses ability to contract opposing weakened muscles. Toomey likens this to the state of a run-down battery, namely, insufficient current comes through the remaining axis-cylinders to produce contraction and therefore the patient moves other intact muscles—not that he loses his sense of movement in the weakened muscles.

This discussion and controversy is interesting, and, while differences of opinion are expressed, the main concept at present in the treatment of poliomyelitis is to restore activity and function of the muscles and prevent the wasting, disuse and contractures so commonly seen after the prolonged use of splints and casts.

STETTENBENZ, Buffalo, N. Y.

STUDIES WITH HEMOPHILUS PERTUSSIS: X. COMPARATIVE ANTIGENIC ANALYSIS OF BACILLUS PARAPERTUSSIS AND HEMOPHILUS PERTUSSIS, PHASE I, WITH CONSIDERATION OF CLINICAL SIGNIFICANCE. EARL W. FLOSDORF, A. BONDI, HARRIET FELTON and AIMS C. MCGUINNESS, J. Pediat. **21**:625 (Nov.) 1942.

Flosdorf and co-workers have shown that the large incidence of parapertussis agglutinins found among the general population is due to specific infections of Bacillus parapertussis and not the result of the minor antigen common both to B. parapertussis and Haemophilus pertussis. The typical disease caused by parapertussis is usually unrecognized clinically except when severe, in which case it resembles mild pertussis. Intensive immunization against pertussis increases the titer of agglutinins against the heterologous species, this effect taking place through the common minor antigen. This antigen causes cross agglutination between B. parapertussis and H. pertussis in phase I. It is not known, however, whether the production of these agglutinins will, through the minor antigen, protect against both parapertussis and true pertussis infections.

Cutaneous tests for susceptibility to pertussis with pure agglutinogen also increases these agglutinins, and the authors suggest their use for production of immunity.

STETTENBENZ, Buffalo.

OBSERVATIONS ON SCHICK TEST REACTIONS AND SERUM ANTITOXIN TITERS AFTER INJECTIONS OF TOXOID. BEN BENJAMIN, GRANT FLEMING and MARY A. ROSS, J. Pediat. **21**:665 (Nov.) 1942.

Benjamin, Fleming and Ross measured quantitatively the levels of diphtheria antitoxin in the serums of children previously immunized with toxoid and attempted to correlate the results with their reactions to Schick tests. They found that no child with less than $\frac{1}{500}$ (0.002) unit per cubic centimeter up to five days after the test gave a definitely negative response to the Schick test. The lowest titer which showed a negative reaction was greater than $\frac{1}{250}$ (0.004) and less than $\frac{1}{100}$ (0.01). The authors also showed that in one group of children who had positive reactions to Schick tests and in whom the antitoxin titer was extremely low the antigenic stimulus of the minute amount of toxin injected in performing the test raised the antitoxin content of the blood serum. Thus, when subsequent Schick tests were done ten to twenty-three months later the reactions were negative and the titer had risen from greater than $\frac{1}{500}$ and less than $\frac{1}{250}$ to greater than $\frac{1}{50}$ and less than $\frac{1}{20}$.

STETTENBENZ, Buffalo.

CEREBROSPINAL FEVER TREATED BY CHEMOTHERAPY: A REVIEW OF 500 CASES TREATED BY CHEMOTHERAPY WITHOUT INTRATHECAL SERUM. G. EMRYS HARRIES, Brit. M. J. **2**:423 (Oct. 10) 1942.

Five hundred cases of cerebrospinal fever are reported in which no intrathecal treatment was given. The mortality in this hospital with intrathecal serum therapy had varied from 1933 to 1937 from 100 to 33 per cent. With the combined use of intrathecal injection of serum and administration of sulfanilamide in 1938 and 1939, mortality had dropped to 13 and 20 per cent. For all persons admitted in this series of cases, even those that died a short time after admission, the mortality was 8.6 per cent. The patients varied in age from 6 weeks to 70 years. In the group between 15 and 25 years there were 104 patients, among whom the mortality was less than 1 per cent. The author presents the following classification, which covers all types of infections he treated: the meningococcic septicemic type, which exhibits the Waterhouse-Friderichsen syndrome, the meningitic and the encephalitic.

In this series of cases stiffness of the neck was observed far more constantly and earlier than the Kernig sign. Also of importance was the fact that a bulging anterior fontanel was an uncommon finding, whereas a fontanel depressed because of vomiting and dehydration was usually present. In only 3 instances in this series was there more than one occurrence of the disease in the same household.

The drugs used were sulfapyridine in 471 cases and sulfathiazole in the remaining 29. Sulfathiazole appeared as effective as sulfapyridine in promoting recovery and was less prone to produce nausea and vomiting. The drugs used were given by mouth whenever this was possible but occasionally had to be given by the nasal route. If for some reason this could not be done, the sodium salt of sulfapyridine was given intravenously. Earlier it had been given intramuscularly, but because of formation of an abscess this method was discontinued.

In these cases fluids were forced vigorously, dextrose and saline solutions being the usual fluids. To patients that had extensive hemorrhages simulating the Waterhouse-Friderichsen syndrome, which included hemorrhages in the adrenal glands, sodium in the form of sodium chloride, and synthetic adrenal cortex extract was given intramuscularly.

In the whole series 66 patients received the dextrose and saline solutions intravenously; in addition, 34 of the patients were given serum intravenously, and 44 were given synthetic adrenal cortex extract intramuscularly. As for reactions to the drug, they were not alarming. Cutaneous eruptions developed in 26 cases, jaundice in 4, cyanosis in 14 and transient hematuria in 3. In no case did agranulocytosis develop. One child died from suppression of urine, probably as a result of renal damage, although permission for postmortem study was not obtained. Although no masks were worn by the attendants, no nurses or physicians attending these patients contracted the disease.

BIRDSONG, University, Va.

ACTIVE IMMUNIZATION BY THE INTRANASAL ROUTE IN EXPERIMENTAL PERTUSSIS. E. A. NORTH and G. ANDERSON, M. J. Australia **2**:228 (Sept. 12) 1942.

The authors' results show that intranasally immunized mice develop a higher grade of immunity against a subsequent intranasal infection with Haemophilus pertussis than do mice immunized with the same antigen by the intraperitoneal or subcutaneous routes. The authors suggest that this immunity is composed of (1) a general specific immunity due to circulating antibodies and (2) a local immunity in the respiratory tract, in which nonspecific factors play a large part. When the vaccines were given intranasally, there was no difference in immunizing power between phase I pertussis vaccines which were heat killed and those to which various antiseptics were added.

GONCE, Madison, Wis.

CLINICAL EXPERIENCE WITH CERTAIN CHEMOTHERAPEUTIC AGENTS IN TREATMENT OF VARIOUS INFECTIOUS DISEASES OF CHILDHOOD. A. STEEGER and others, Rev. chilena de pediat. **13**:139 (Feb.-March) 1942.

In an extensive review of this field the authors conclude that sulfapyridine and especially sulfadiazine are the most effective agents in the treatment of meningococcic and pneumococcic meningitis. Sulfanilamide is effective in the treatment of erysipelas, particularly when it appears in the young infant or nursling. It also has a specific effect on gonococcic conjunctivitis. It shortens the treatment, and there are few complications.

The chemotherapeutic drugs have no action on infectious pemphigus. Sulfaguanidine has a rapid effect on bacillary dysentery in young infants; along with it must be given adequate dietary treatment.

The action of sulfapyridine is often specific against pneumonia. It shortens notably the afebrile course and apparently prevents relapses and the occurrence of empyema.

The action of sulfapyridine is doubtful in certain types of bronchial pneumonia and peribronchitis. In these disorders there is also marked intolerance to the drug. The dosage and the route of administration depend on the causation of the infection and on its gravity. In general one should not give an initial dose of more than 0.3 to 0.4 Gm. per kilogram of body weight.

It is always well to extend the treatment some days beyond disappearance of the fever and of the clinical signs.

The greatest number of toxic symptoms or symptoms of intolerance to the drug were shown with sulfapyridine and caused nausea, cyanosis, hematuria, exanthemas and anemia. In cases of severe illness the treatment must be supplemented by blood transfusions and liberal administration of fluids.

SCHLUTZ, Chicago.

Acute Infectious Diseases

EXPERIMENTAL EOSINOPHILIA WITH KERATIN FROM ASCARIS SUUM AND OTHER SOURCES. DAN H. CAMPBELL, J. Infect. Dis. **71**:270 (Nov.-Dec.) 1942.

The experiments performed demonstrate the eosinophilotactic properties of fractions of keratin from several helminths but fail to substantiate previous reports that other types of proteins or lipids show this property. This property is not unique for keratin from helminths, but is also shown by keratins from a variety of sources as well as by heat-coagulated ovalbumin. These substances are not eosinophilotactic per se but produce an eosinophilia after a single

injection because they remain in the body after antibodies are formed, giving rise to hypersensitive responses. The activity of these substances in relation to insolubility, antigenicity and the presence of sulfhydril groups is discussed.

TOOMEY, Cleveland. [AUTHOR'S SUMMARY]

ENTEROBIASIS IN CHILDREN. ALVIN H. JACOBS, J. Pediat. **21**:497 (Oct.) 1942.

Jacobs describes a unique method of diagnosing enterobiasis through the use of Scotch cellulose tape. The tape is folded over a wooden tongue depressor with the sticky surface outward. This is used as an applicator and applied to the perineal folds; the eggs are readily picked up. The tape is then removed and spread out, adhesive surface down, on a glass microscope slide. It may then be examined at leisure under the low power of the microscope without the use of a cover slip.

Using this method, Jacobs examined 228 unselected clinic children. In 31.3 per cent pinworm eggs were found. Of these infected patients 41 per cent had symptoms of repeated abdominal pain; 49 per cent were "nervous"; 41 per cent were underweight; 38.6 per cent were poor sleepers; 38.6 per cent had anorexia; 21.3 per cent suffered from pruritus ani, and 17.3 per cent had enuresis. Of 40 infected girls, 27.5 per cent had a vaginal discharge.

STETTENBENZ, Buffalo.

STUDIES ON AIR-BORNE INFECTION IN A HOSPITAL WARD: I. THE EFFECT OF ULTRAVIOLET LIGHT ON CROSS-INFECTION IN AN INFANTS' WARD. HARRIET E. SOMMER and JOSEPH STOKES JR., J. Pediat. **21**:569 (Nov.) 1942.

It has been shown experimentally that ultraviolet irradiation can destroy air-borne droplet nuclei containing pathogenic bacteria, and it has been of value in cutting down air-borne infection in hospital wards and operating rooms. Sommer and Stokes used ultraviolet irradiation in an open ward which was connected by a long corridor to a nonirradiated control ward. Samples of air were taken and analyzed for bacteria. Also clinical evidence of cross infection was determined.

It was found that the irradiation was definitely effective in reducing the number of air-borne organisms, and it was of interest that air in the control ward that had apparently circulated through the corridor from the irradiated ward also showed low bacterial counts. Little cross infection occurred in either ward, and that which did apparently was due to the connecting corridor.

The authors recognize, however, that uncontrollable factors may enter into a study of this nature. Visitors to the wards and children removed to other parts of the hospital and back again to the wards may bring in organisms.

STETTENBENZ, Buffalo.

STUDIES ON AIR-BORNE INFECTION IN A HOSPITAL WARD: II. EFFECTS OF ULTRAVIOLET IRRADIATION AND PROPYLENE GLYCOL VAPORIZATION UPON THE PREVENTION OF EXPERIMENTAL AIR-BORNE INFECTION OF MICE BY DROPLET NUCLEI. WERNER HENLE, HARRIET E. SOMMER and JOSEPH STOKES JR., J. Pediat. **21**:577 (Nov.) 1942.

In this interesting experiment Henle, Sommer and Stokes exposed groups of mice in a large hospital ward containing sixteen cubicles to atomizer-sprayed streptococci of the Lancefield group C and atomized virus of influenza A. The effectiveness of ultraviolet irradiation and of propylene glycol vapor were compared as to their disinfectant ability.

Most mice readily succumbed to large concentrations of streptococci (usually over 3,000 per cubic foot [84.9 cubic meters] of air), the mice dying of streptococcic pneumonia and septicemia. Propylene glycol protected them completely, as did ultraviolet irradiation. With low concentrations (200 to 500 organisms per cubic foot of air) all mice survived, and cultures from the lungs taken ten days later revealed no streptococci. It was of interest that mice exposed to these concentrations became carriers. Propylene glycol and ultraviolet irradiation were similarly effective in protecting against influenza A.

STETTENBENZ, Buffalo.

DIAGNOSIS AND MANAGEMENT OF SEVERE INFECTIONS IN INFANTS AND CHILDREN: A REVIEW OF EXPERIENCES SINCE THE INTRODUCTION OF SULFONAMIDE THERAPY; II. HEMOLYTIC STREPTOCOCCAL MENINGITIS. ALEXIS F. HARTMANN, DOROTHY WOLFF, FRANCES M. LOVE and BARBARA S. KENDALL, J. Pediat. **21**:591 (Nov.) 1942.

Twelve cases of hemolytic streptococcus meningitis are reported in detail. There were 4 deaths; 3 of them, however, occurred in children moribund on admission. The corrected mortality was thus 11 per cent. The fact is stressed that in the majority of these cases the infection occurs as a complication of a neglected infection of the respiratory tract, usually an infection of the temporal bone. One case in particular was of interest in that the meningitis

developed two months after bilateral simple mastoidectomy. Early correct diagnosis in these cases is of great importance, and no hesitation should be made in performing lumbar puncture. Sulfanilamide, sulfapyridine and sulfadiazine are the drugs of choice in treatment and should be given in large doses to insure adequate concentrations in the spinal fluid. Sulfanilamide is particularly valuable because it may so readily be given subcutaneously or intravenously and because it is compatible with all solutions likely to be given intravenously. Administration of these drugs should be continued until complete recovery, for, although the spinal fluid is quickly sterilized, infection may persist in the temporal bone. The authors believe in making frequent analyses of the spinal fluid to determine the course of the disease.

STETTENBENZ, Buffalo.

INHIBITING EFFECT OF METHIONINE, CHOLINE AND BETAINE ON RABBIT'S SUSCEPTIBILITY TO INFECTION WITH VACCINIA. DOUGLAS H. SPRUNT, Proc. Soc. Exper. Biol. & Med. **51**:226 (Nov.) 1942.

Previous experiments revealed that subcutaneous injections of methionine increased the resistance of rabbits to dermal infection with vaccinia. In the present study a similar effect was exhibited by choline and less by betaine. If the observed effects are proved for other viruses and other animals, the author believes that it is possible that a chemotherapeutic agent effective against viral infection may be discovered among these or related chemical substances.

HANSEN, Minneapolis.

CLINICAL ASPECTS OF THE DIAGNOSIS OF RHEUMATIC DISEASE. E. CIENFUEGOS, Rev. chilena de pediat. **13**:228 (Feb.-March) 1942.

The author states that in early childhood rheumatic disease has an extraordinary polymorphism. The polyarticular forms of this disorder occur more frequently as the infant advances in age.

The actual infectious agent is somewhat obscure. Frequent forms of rheumatism observed are abdominal types resembling typhoid or pseudomeningitis. Monoarticular forms are often found. They are observed in ambulatory patients and are often accompanied by cardiac complications.

The author reports that cardiac infections in infancy are frequently due to rheumatic disease and that a minute examination of the heart at this age often gives the key when the diagnosis is doubtful. He considers the determination of the sedimentation rate an indispensable laboratory procedure, both for the diagnosis of the condition and because of the information it gives with regard to its evolution and progress. He states that a study of the eosinophil picture of the blood during the evolution of the rheumatic syndrome is important. A study of the leukocytic count of the red blood cells is of less account.

SCHLUTZ, Chicago.

MEDICAL AND SOCIAL MEASURES IN THE PROPHYLAXIS AND TREATMENT OF RHEUMATIC DISEASE. M. ACUNA and A. PUGLISI, Rev. chilena de pediat. **13**:269 (Feb.-March) 1942.

The authors discuss the etiologic factors which play a role in the development or the incidence of rheumatic disease and which must be considered in its prophylaxis and treatment. Climatic conditions have a leading part in its causation. The disease is infrequent and almost nonexistent in warm and dry climates and has a high incidence in colder climates with high humidity.

Other factors, such as heredity, predisposition, nutrition, hygienic conditions and environmental factors are important. Focal infections play a major role. Many of these factors can be eliminated by timely action and enter largely into a prophylactic program. The patient with potential rheumatic disease or one already affected with the disease should be under careful control and supervision. The authors plead for the establishment of clinical centers and consultation or hospital service adequately equipped to care for and supervise the child threatened or affected with the disorder. Such centers are established in Buenos Aires and other parts of Argentina and function with great success.

The patient with rheumatic disease is referred when the first attack occurs. These centers are then concerned with selection of the proper climate, elimination of foci of infection, improvement of the hygienic environment, active medical control of the infection, periodic check of the sedimentation rate and constant medical supervision.

If chronic cardiac complications have arisen or are present in the case, there is constant control of the environment by the visiting nurse. Periodic examinations are made at special centers, and attempts are made to get proper social adjustment of the patient. There are repeated checks of the patient by expert cardiologists. The results with this type of prophylaxis and treatment of patients with rheumatic and cardiac diseases have been remarkably successful.

SCHLUTZ, Chicago.

PROPHYLACTIC TREATMENT OF RHEUMATIC DISEASE IN THE CHILD. J. M. MACERA, A. P. RUCHELLI and R. GAIG, Rev. chilena de pediat. **13**:278 (Feb.-March) 1942.

The authors recommend complete rest in bed the moment rheumatic disease has been diagnosed or even suspected. The drugs used in the treatment of this disorder are the salicylates and aminopyrine. The salicylates are given in rather massive doses—0.1 to 0.2 Gm. per kilogram of body weight. Two or three times this amount can be given for the more active infections.

It is usually best to give the salicylate preparations with some alkali, such as sodium bicarbonate or magnesium oxide or carbonate. The authors have found aminopyrine five or six times as potent as salicylates. It is well tolerated by the digestive tract but presents the danger of causing agranulocytosis during prolonged use. The authors have never administered a maximum dose of more than 1.2 Gm. per day to children under 15 years of age. This amount is divided into four doses through the day.

The authors have found vaccines, other antistreptococcic preparations and other remedies for rheumatic fever ineffective. Blood transfusions have sometimes been useful in cases of severe and resistant symptoms. The authors have seen no good effect of use of sulfonamide compounds in the treatment of acute rheumatic phases. In cases of cardiopathy with signs of circulatory decompensation the authors feel that the use of digitalis is indicated only when the cardiac insufficiency has produced symptoms of chronic congestive failure and auricular fibrillation. Digitalis must be used with caution, and the amount given should seldom exceed 4 cg. per day per kilogram of body weight.

For patients who have enlargement of the liver, ascites and edema, the authors recommend mercurial diuretics, such as mersalyl. Sedatives and hypnotics must be used if the patient has considerable cardiac involvement accompanied by precordial pain.

The convalescent treatment of the patient with rheumatic disease is important, and the authors feel that a carefully regulated program of activity is absolutely essential. The authors recommend the removal of focal infection during the period of convalescence, provided that the patient has made satisfactory progress and is at the moment not showing dangerous symptoms.

The rheumatic disorder must be in a relative stage of inactivity at the time. This applies particularly to the removal of tonsils and adenoids. A change to a warm, dry climate is extremely beneficial.

The authors state that rheumatic disease presents social aspects and is in many respects probably a preventable disease. With the widespread disorder in many countries, this condition becomes a problem of public health and one in which the state should have concern. Prophylactic measures which prevent the onset of the disorder can be effectively provided by improving environmental and hygienic conditions, and one of the most essential is the provision of adequate hospital care and convalescent center care for persons with the disease. Hospital centers or so-called "antirheumatic" centers should be liberally provided throughout the country. Where this has been done a remarkable reduction in the number of cases of this disorder has been effected.

SCHLUTZ, Chicago.

ACUTE RHEUMATISM. A. E. WALTHER CASAL and P. ELIZALDE, Rev. chilena de pediat. **13**:291 (Feb.-March) 1942.

This article presents an exhaustive review by the authors of all pathologic data reported in the world literature in studies of acute and chronic rheumatic disease and adds to it their own observations. In covering the subject they follow the classification adopted by the Argentine Rheumatism Centers and the International League of Amsterdam, which is as follows:

I. Acute Rheumatism

II. Chronic Rheumatism

1. Articular
   - A. Subchronic rheumatoid arthritis
   - B. Rheumatoid or metastatic arthritis
   - C. Arthritis due to climate
   - D. Osteoarthritis
   - E. Spondylitis
     - (a) rheumatoid
     - (b) osteoarthritic

2. Nonarticular—Fibrositis

Many good illustrations of pathologic material accompany this exhaustive and instructive review.

SCHLUTZ, Chicago.

PRESENT DAY CONCEPT OF THE ETIOLOGY AND PATHOGENESIS OF RHEUMATIC DISEASE. J. D. LUQUE,, Rev. chilena de pediat. **13**:318 (Feb.-March) 1942.

The germ or the virus which causes rheumatic disease has as yet not been demonstrated. It does not seem to cause a specific infection but is rather polyvalent in action.

Hemolytic streptococci play an important role in this disease and are generally resident in the lymphatic system.

The disease seems to be one of "reaction" or of some allergic response to infectious agents and their toxins.

Acute rheumatic disease is a manifestation of intense allergic phases.

SCHLUTZ, Chicago.

Chronic Infectious Diseases

GASTRIC LAVAGE IN THE CONTROL OF TREATMENT OF PULMONARY TUBERCULOSIS. JOSEPH J. FURLONG and MARY K. WARREN, Am. J. M. Sc. **204**:674 (Nov.) 1942.

The authors report on a total of 1,414 gastric lavages done on 491 adult patients with tuberculosis. Of this number, 180 patients had tubercle bacilli in their gastric contents on at least one examination. An analysis is presented of these 180 patients with bacilli in the material obtained at gastric lavages.

The duration of organisms in the gastric contents after the sputum has become sterile was determined in 57 cases. In 90 per cent of this group the results of cultures of material obtained by lavage and of guinea pig inoculations were negative in less than two years; the average time for the entire group was eleven months.

Of a group of 50 patients treated by collapse therapy, 86 per cent had sterile gastric contents and negative results of guinea pig inoculation in less than two years, with an average interval of eight and one-half months.

HENSKE, Omaha.

THE MANAGEMENT OF THE MINIMAL TUBERCULOUS LESION. ALFRED L. KRUGER, BENJAMIN P. POTTER and ABRAHAM E. JAFFIN, Am. Rev. Tuberc. **46**:50 (July) 1942.

A total of 185 patients were followed in this study, of whom 110 were classified as having a productive and 75 an exudative infiltrate. Seventy-nine of the former and 23 of the latter were between the ages of 5 and 24 years. Seventy-eight per cent of the exudative lesions were found in patients between the ages of 10 and 29 years. Patients with productive lesions were fairly equally distributed throughout all age groups. Supporting the authors' advocacy of the value of rest in bed as the initial procedure in the treatment of minimal tuberculosis were the results of such treatment as applied to the patients observed in this study. Of their hospitalized patients, 78 per cent with exudative lesions and 96 per cent with productive lesions were effectively treated in this manner. Of patients treated in the clinic similar results were obtained in 58 per cent with exudative and in 100 per cent with productive lesions. It is to be understood, however, that in dealing with advanced tuberculosis collapse therapy should not be delayed. It is definitely indicated when a progression of the lesion occurs, when bacillus-containing sputums are recovered which fail to become sterile after a liberal period of rest in bed or when hemoptysis is present. When such symptoms develop, one should suspect the presence of small "hidden" cavities and hence of moderately advanced tuberculosis. In certain instances these cavities may be visualized by means of fluoroscopy in the oblique positions, by roentgenograms in the anteroposterior projection instead of posterior-anterior or by laminography. If a cavity is found, pneumothorax is indicated.

EUGENE SMITH, Ogden, Utah.

THE CLINICAL EPISODE IN TUBERCULOSIS AND THE METEOROLOGICAL ENVIRONMENT. WILLIAM F. PETERSEN, Am. Rev. Tuberc. **46**:407 (Oct.) 1942.

A series of case records are analyzed, and the association of precipitation of clinical symptoms with the meteorologic situation at the time is made evident. These interrelations are not specific for tuberculosis and can be observed in every patient. The human organism is constantly pendulating in a biologic rhythm that is largely conditioned by the atmosphere, though many other forces are also active. On the labile organism these environmental forces bring about increased or decreased resistance, increasing and decreasing hydration, increase or lessening of p_H levels, of ionization of calcium, of levels of lipids, of maturation of leukocytes, of permeability of capillaries, and of levels of pressor substances. When they are generally understood, a consideration of these factors in relation to the diseased person should materially facilitate the evaluation of the clinical picture, the management of the patient and the prognosis.

SMITH, Ogden, Utah.

SPIROCHAETAL SURVIVAL IN FROZEN PLASMA. MARK M. RAVITCH and JOHN W. CHAMBERS, Bull. Johns Hopkins Hosp. **71**:299 (Nov.) 1942.

This study was carried out because of the increasing popularity of blood banks.

Human and rabbit plasma heavily inoculated with Treponema pallidum and frozen at —20 C. for forty-eight hours or longer is not infectious for normal rabbits. The material is infectious, however, when the freezing period is only twenty-four hours. Under these conditions the incubation period is prolonged, even though the experimental animals receive an inoculation dose twice the size of that given the controls.

LYTTLE, New York.

ASPHYXIATED BACTERIA AS A VACCINE IN TUBERCULOSIS. TRUMAN SQUIRE POTTER, J. Infect. Dis. **71**:232 (Nov.-Dec.) 1942.

Avian tubercle bacilli when completely deprived of virulence by asphyxiation, without the use of coagulating heat, retain constituents able to confer on the rabbit considerable, though as yet incomplete, protection against infection with virulent avian tubercle bacilli.

TOOMEY, Cleveland. [AUTHOR'S SUMMARY]

NONSPECIFIC SEROLOGIC REACTIONS FOR SYPHILIS IN INFANTS AND CHILDREN. ALLEN HILL, J. Pediat. **21**:207 (Aug.) 1942.

A ten year survey of serologic data was made from records of children admitted to the Infants' and Children's Hospitals, Boston. The Hinton and the Davies-Hinton test were used exclusively. In all, 26,700 tests were made. Negative reactions were obtained in 26,645 tests on presumably nonsyphilitic patients. Two hundred and forty-two nonspecific reactions, positive and doubtful, were recorded. Acute infections in general produced these false positive reactions.

STETTENBENZ, Buffalo, N. Y.

ACTINOMYCOSIS. CHARLES PICKNEY, Proc. Roy. Soc. Med. **25**:686 (Aug.) 1942.

Pickney reports a case of actinomycosis in a boy aged 12 years.

WILLIAMSON, New Orleans.

RUPTURE OF A LARGE CAVERN IN THE COURSE OF PNEUMOTHORAX. D. SANS FONSECA, Bol. Soc. cubana de pediat. **14**:477 (Sept.) 1942.

The author states that insufficient collapse is the most frequent cause of the complications which present themselves in pneumothorax and that insufficient pneumothorax is more dangerous than useful and must be improved by better treatment or not used at all.

Therapeutic collapse should not be routinely employed. The socioeconomic condition of the patient, his general state of health, his age, the condition of his cardiovascular apparatus and the type of his lesion are all factors determining when it should be used.

Pleuropulmonary perforation with a following purulent exudate is a grave complication which has a somber prognosis.

The author illustrates these points in the report of a case in a white child aged 13 years affected with tuberculosis and on whom a pneumothorax had been performed, with the resulting development of unfavorable symptoms due to the rupture of a huge cavity into the pleura.

SCHLUTZ, Chicago.

THE FIRST INFECTION OF PULMONARY TUBERCULOSIS, FROM THE ROENTGENOLOGIC AND THE ANATOMIC POINT OF VIEW. NAFTALI RODRIGUES, Prensa med. mex. **7**:93 (July 15) 1942.

The first infection with tuberculosis begins with the fixation of the bacillus of Koch in the human organism and terminates when the tendency to dissemination ceases, which happens from seventeen to twenty-four months after infection. The primary infection occurs in healthy people; reinfection occurs in those who have been sensitized to tuberculosis.

When the germ of tuberculosis enters the lungs, by air or blood stream, it causes a reaction; the histiocytes enclose the germs and carry them to the alveolus, where they are released, and they find their way to the walls of the alveolus. The alveolar cells act as phagocytes. The initial lesion is usually spherical and may present in its environs small nodules. The size of the initial lesion varies—it may be that of the head of a pin, a millet seed, a pea, a hazelnut or a mandarin. It may invade the entire lobe or even the entire lung.

These lesions may be classified as nodular or infiltrated. The nodules usually develop into the alveoli of the lung as secondary to alveolitis. The histiocytes of the alveolus are transformed into giant cells with many nuclei. The perifocal infiltration tends to disappear completely.

The first infection of pulmonary tuberculosis tends to disappear totally, or is reduced to a fine fibrosis, fibrous waxy or waxy condition. The lesion of tuberculosis may extend by the bronchi, blood or lymphatics.

GIFFEN, Toledo, Ohio.

Diseases of Blood, Heart and Blood Vessels and Spleen

CONGENITAL PULMONARY STENOSIS WITH CLOSED CARDIAC SEPTA. R. E. GARRISON, Am. Heart J. **24**:685 (Nov.) 1942.

The author reports a case of congenital pulmonary stenosis with closed septums. The patient was a 15 year old girl who had had dyspnea and cyanosis for two years. Clubbing of the fingers was present. A systolic thrill and murmur were present over the precordium. The arm to tongue circulation time was ten seconds. The antemortem diagnosis was pulmonary stenosis with interventricular septal defect.

The author points out that the normal circulation time should have led to consideration of pulmonary stenosis without septal defect, for when a septal defect is present the circulation time from the arm to the tongue is greatly shortened.

GIBSON, Chicago.

THE INFLUENCE OF DIET ON THE PHYSIOLOGIC ANEMIA OF INFANTS. KATHERIN F. BROKAW, MARGARET S. SEDAM and ANNE MARIE CASSIRER, J. Pediat. **21**:769 (Dec.) 1942.

In a two year study made in a clinic for well babies the authors investigated the effect of early introduction of solid foods on the physiologic anemia occurring usually in the sixth to the ninth month. The solid food introduced earliest, at 8 weeks, was strained vegetables; cereals and egg yolk were introduced at 12 weeks, and potato, meats and fruits were fed at 5 months. This was the diet for the advanced group. Two other groups had foods introduced at later dates. No appreciable effect on hemoglobin levels or on red blood cell counts occurred in the advanced feeding group, but it was the impression of the authors that gain in weight and height and increase in muscle tone were better in this group. The foods were taken well, and there were few allergic reactions.

STETTENBENZ, Buffalo.

HEMOLYTIC TRANSFUSION REACTIONS DUE TO THE RH FACTOR: A PREVENTABLE DANGER. LOUIS K. DIAMOND, New England J. Med. **227**:857 (Dec. 3) 1942.

After discussing the development and recognition of the Rh factor in the blood, Diamond presents brief case histories of 10 patients who suffered hemolytic transfusion reactions. In every case, the recipient received compatible blood according to grouping and cross matching by the ordinary methods. Later investigation disclosed that the incompatibility involved the Rh factor. This factor was absent from the blood of each recipient, and through the development of isoimmune bodies to the Rh factor a hemolytic reaction occurred when blood containing the factor was administered.

Isoimmunization occurred in some patients as the result of previous transfusions with blood containing the Rh factor; in others, as the result of pregnancy involving a fetus having Rh blood cells that contained the Rh factor. In still another patient, an anti-Rh agglutinin of natural origin seemed to be present.

Following the hemolytic reaction, the use of blood without the Rh factor for subsequent transfusions in each patient resulted in no further difficulties.

GENGENBACH, Denver.

Diseases of Lungs, Pleura and Mediastinum

ACUTE PUTRID PULMONARY ABSCESS: THE CRITERIA OF CURE. ARTHUR S. W. TOUROFF and HAROLD NEUHOF, Am. Rev. Tuberc. **46**:121 (Aug.) 1942.

Remission of symptoms is common during the acute stage of putrid pulmonary abscess owing to the establishment of drainage into the bronchial tree. This may result in diminution of fever and lessening of expectoration and fetor. This amelioration of symptoms may lead the medical attendant to assume that a cure has been affected. In certain cases this may be true, but in others the improvement may be only temporary and the patient may later appear for treatment in the subacute or chronic stage of the disease. It is important, therefore, that definite criteria of cure be established, since all observers agree that regardless of the treatment employed the longer the duration of the abscess the higher the morbidity and mortality and the lower the incidence of satisfactory results. Regardless of the subsidence or disappearance of clinical symptoms, no pulmonary abscess should be considered cured unless a roentgenogram of the chest reveals not only the disappearance of the abscess cavity but of all pulmonary infiltration. For this purpose, roentgenograms in the posteroanterior, lateral

and at times oblique projections are necessary. The abscess should not be considered cured until the fluid level has disappeared and the "rim," or wall of the cavity, has been absorbed.

Occasionally, especially in patients who have been subjected to operation, abnormal shadows may be seen on the roentgenogram after the patient is free from symptoms and cavity and pulmonary infiltration have disappeared. In such cases, diagnostic bronchoscopy should be performed.

When the stated criteria of cure have been met, complete healing can be said to have taken place. Under such circumstances recurrence has never been noted.

EUGENE SMITH, Ogden, Utah.

HAEMORRHAGE FROM THE TRACHEA, BRONCHI AND LUNGS OF NONTUBERCULOUS ORIGIN. CHEVALIER L. JACKSON and SIDNEY DIAMOND, Am. Rev. Tuberc. **46**:216 (Aug.) 1942.

Short cuts and diagnosis by inference in patients with hemoptysis are beset with many pitfalls. The symptoms accompanying the hemorrhage may give valuable information. As has been pointed out, in hemoptysis with massive hemorrhage, pallor and loss of consciousness are likely to precede the appearance of blood, whereas in profuse bronchopulmonary hemorrhage the blood is almost invariably expectorated before signs of acute loss of blood appear. Should there be any question of the origin of the hemorrhage, an investigation of the esophagus, stomach and duodenum is indicated. Too much emphasis has been placed on varicose veins at the base of the tongue as hemorrhagic foci. In the vast majority of cases of spitting of blood in the absence of vomiting or regurgitation, the blood is brought up from the lower respiratory tract. While the history and physical observations may suffice to establish the lower respiratory tract as the source of the bleeding, precise localization of the lesion requires fluoroscopic and roentgenographic examination and often bronchoscopy. In this series of cases a hemorrhagic focus could be seen on bronchoscopic examination of 25 per cent of the patients. Most of the neoplasms causing hemoptysis were readily seen with the endoscope, while in the case of inflammatory lesions the bleeding point was seldom seen. The precise cause could not be determined in nearly one fourth of the patients. The observations in this study, however, indicate that hemoptysis of nontuberculous origin has its foundation in an inflammatory process much more often than in a neoplasm.

In this group of 436 nontuberculous patients with tracheal, bronchial and pulmonary bleeding, 66 had their initial spitting of blood before the age of 20 years and 44 of these had bronchial dilatations.

EUGENE SMITH, Ogden, Utah.

THE SIMILARITY OF CYTOPLASMIC INCLUSIONS IN INFANT PNEUMONITIS AND BOVINE EPITHELIAL CELLS. JEAN BROADHURST, M. ESTELLE MACLEAN and E. H. PETERSON, Cornell Vet. **32**:390 (Oct.) 1942.

The author studied specimens collected from the mouths of cows at the time of slaughter. The cells of the epithelial strips taken from the depressions between the larger fungoid papillae of the cheek were found to contain numerous inclusion bodies similar to those reported in hospital epidemics of primary virus pneumonitis in young infants. Photomicrographs from both sources demonstrate the similarity. It is suggested that milk may be contaminated by the saliva of infected cows.

LESLIE, Evanston, Ill.

CONSIDERATION OF THE RESPIRATORY PATTERN AS A PREDISPOSING FACTOR IN THE ETIOLOGY OF PNEUMONIA. W. J. NUNGESTER, ROY G. KLEPSER and ALICE H. KEMPF, J. Infect. Dis. **71**:57 (July-Aug.) 1942.

The authors report that data support a hypothesis that the relative force of inspiration and of expiration may be a factor in determining whether mucus is aspirated or forced outward. The data include results of studies on the aspiration of ink particles and on the production of pneumococcic pneumonia in rats in experiments in which the respiratory pattern was altered.

TOOMEY, Cleveland.

IDENTIFICATION OF TWO STRAINS OF VIRUS ISOLATED FROM CASES OF ATYPICAL PNEUMONIA. M. DORTHY BECK and MONROE D. EATON, J. Infect. Dis. **71**:97 (Sept.-Oct.) 1942.

The authors describe two new strains, P and B, of virus from 2 patients with atypical pneumonia, which were identical with strain S-F (previously described). These strains present group antigenic relationship with certain other viruses, i. e., meningopneumonitis (strain MP-F97), psittacosis and lymphogranuloma venereum, though not antigenically identical with any of these viruses.

A laboratory accident experienced by a patient with meningopneumonitis virus probably had no relation to the subsequent infection, the cause of which was proved by isolation and study of the strain B.

TOOMEY, Cleveland.

THE WELTMANN REACTION IN RESPIRATORY DISEASES IN CHILDREN. SUSAN C. DEES and HENRY MORTON, J. Pediat. **21**:514 (Oct.) 1942.

The Weltmann serum coagulation reaction was determined on 500 children for whom a definite clinical or pathologic diagnosis was made. The authors feel that this is a valuable and reliable test. The reaction is constant in normal healthy persons, and their serum has a coagulation band of 6; in the presence of infection or pathologic processes definite deviations from this value occur. It is uninfluenced by dehydration, acidosis or alkalosis, allergy or anemia.

The authors' summary of the effects of respiratory infection on the Weltmann reaction is as follows:

"2. The coagulation band is shortened below the normal value of six in the presence of infection and is increased with recovery.

"3. In mild respiratory infections the coagulation band is slightly shortened; values of four and five are found.

"4. In lobar pneumonia, at the onset, the coagulation band is zero and remains low until recovery is well established.

"5. Bronchopneumonia has no characteristic band; the values range from zero to four.

"6. In bronchial asthma the coagulation band is six unless there is some coexisting infection, which shortens the band."

STETTENBENZ, Buffalo.

DISCUSSION ON THE PREVENTION OF CHRONIC LUNG DISEASES IN CHILDHOOD. Proc. Roy. Soc. Med. **35**:689 (Aug.) 1942.

Dr. Alan Moncrieff included in the conditions which he called "chronic lung diseases" chronic and recurrent bronchitis and the group known variously as chronic pneumonia, pulmonary fibrosis, unresolved pneumonia and damaged lung—all tending to end in bronchiectasis. Two considerations, infection and resistance, were first taken up and the following questions were asked: Is anything being done to prevent droplet infection in the home, in the school and in the institutions? Is the public being sufficiently educated in the use of handkerchiefs and masks, also in ventilation? Is anything being done to build up the child's resistance? Is anything being done to deal with tonsils, adenoids and sinus infections from the preventive aspect? Is the diet of the child adequate? There appears to be a vicious circle—chronic infection → undernutrition → chronic infection.

Acute pulmonary conditions frequently do not clear up properly and are frequently followed by chronic lung disease. So the diseases causing the acute condition in the lungs, such as measles and pertussis, should be prevented. The use of pertussis vaccines and the use of blood for modifying measles should be carried out by public health officers on a wide scale.

Collapse of the lung, the speaker stated, is far more common than is generally supposed and may be due to sticky sputum produced by the injudicious use of atropine and too little fluid in acute pulmonary conditions. Tuberculosis must be excluded, because in far too many cases a collapsed lung was disastrously treated by passive measures available for tuberculosis. Hence if the severer types of chronic pulmonary disease are to be prevented every person with chronic pulmonary infection should have a patch test followed by roentgen examination, a bronchogram with a contrast medium and bronchoscopy in that order.

Dr. C. Elaine Field and Dr. Nora I. Wattie also discussed the problem at length.

WILLIAMSON, New Orleans.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

THE MODE OF THE LAXATIVE ACTION OF PHENOLPHTHALEIN. PHILIP BLICK, J. B. BERARDI and OSKAR WOZASEK, Am. J. Digest. Dis. **9**:292 (Sept.) 1942.

The authors conclude that phenolphthalein is not an intestinal irritant as judged by standards they set up. They also state that phenolphthalein acts directly on the muscle and support their conclusion by the following facts:

(*a*) Atropine, which paralyzes the motor nerves of the intestine, does not stop the cathartic action of phenolphthalein.

(*b*) Phenolphthalein does not affect parasympathetic nerves, as judged by its effect on the vagus mechanism of the heart.

(*c*) Drugs like physostigmine, which stimulate the intestine through the nerves, also affect the vagus nerve to the heart in a similar manner.

Barum chloride and solution of posterior pituitary, which act on musculature when applied locally, affect the intestine in a manner similar to, but more severely than, phenolphthalein.

LESLIE, Evanston, Ill.

CHRONIC GASTRIC ULCER IN A SIX YEAR OLD CHILD. MANFRED KRAEMER and LESLIE TOWNSEND, Am. J. Digest. Dis. **9**:338 (Oct.) 1942.

At the age of 5 years the patient began to complain of pain in the left upper quadrant of the abdomen lasting four or five minutes, usually before or during breakfast. It would then disappear for intervals of a few days. In January 1942, the pain was present every morning for one week. Vomiting occurred once, but there were no other symptoms, nor was there any abdominal tenderness. With the patient standing after a teaspoon of a solution of barium sulfate had been swallowed a niche could be seen on the posterior gastric wall in the body of the stomach. When the stomach was filled with barium, the niche could not be demonstrated. With the establishment of a regimen for the relief of ulcer, the pains ceased and occult blood disappeared from the stools. In roentgenograms taken a month later the niche was not seen. This is probably the eighth case of gastric ulcer reported in children between the ages of 2 and 6 years and the twenty-sixth in children between the ages of 2 and 12 years.

LESLIE, Evanston, Ill.

CONGENITAL ANOMALIES OF THE PRIMARY MIDGUT LOOP. JOSEPH M. MILLER and E. G. WAKEFIELD, Am. J. Digest. Dis. **9**:383 (Nov.) 1942.

These anomalies divide themselves into six groups: (1) congenital umbilical hernia, (2) defects of the vitelline duct, (3) anomalies of position, (4)) abnormalities resulting from traction bands, (5) results of inadequate fixation and (6) anomalies due to incomplete peritoneal fusion. Cases are cited illustrating each of these groups. Four patients were in the pediatric age group. The first was a newborn child in whom the sac of an umbilical hernia had ruptured and part of the small bowel was protruding through the rent. The second was a 2 year old boy in whom there had been a discharge from the umbilicus with some episodes of bleeding. Removal of the remnants of the vitelline duct afforded complete relief. The third was a boy of 9 years whose appendix was on the left side. The fourth was a youth of 19 who had partial obstruction due to a traction band across the duodenojejunal junction.

LESLIE, Evanston, Ill.

DEPRESSION OF GASTRIC MOTILITY WITHOUT ELEVATION OF BODY TEMPERATURE FOLLOWING THE INJECTION OF PYROGENS. H. NECHELES, P. DOMMERS, M. WEINER, W. H. OLSON and W. RYCHEL, Am. J. Physiol. **137**:22 (Aug.) 1942.

In the assay of substances which depress gastric motility authors have been careful to state whether or not such substances affected body temperature. It seems to be the consensus that slight elevations of body temperature do not affect gastric motility, while considerable elevations will depress it. It seems to Necheles and his associates that in the light of their present results this opinion ought to be revised.

The effects of doses of pyrogenic substances so small that they would not produce elevation of body temperature in a dog were tested on gastric motility stimulated by prostigmine methylsulfate. In a great number of experiments, depression of gastric motility resulted with no change in rectal temperature and with no subjective signs in most of the dogs. The relation of this finding to dyspepsia during colds and other infectious diseases in which no elevation or only a slight elevation of body temperature occurs is discussed.

NOURSE, Cleveland.

SOLITARY NONPARASITIC CYST OF THE LIVER. H. STOKES MUNROE JR., Ann. Surg. **116**:751 (Nov.) 1942.

The author reports on the surgical treatment of a solitary nonparasitic cyst of the liver occurring in a 9 month old child.

Nonparasitic cysts of the liver may be single or multiple and commonly are associated with cysts of other organs. They occur more often in females. The external surface of the cyst is usually smooth and glistening.

Solitary nonparasitic cysts of the liver usually grow so slowly that few symptoms are produced, advice usually being sought because of the presence of a painless abdominal swelling.

Sudden onset of acute symptoms suggests hemorrhage into the cyst, suppuration or twisted pedicle in the pedunculated variety. A correct preoperative diagnosis is rarely made.

The only treatment for solitary cysts of the liver demanding relief is surgical intervention.

BANTIN, Omaha.

THE EFFECT OF HYDROCHLORIC ACID ON THE PYLORIC SPHINCTER, ON THE ADJACENT PORTIONS OF THE DIGESTIVE TRACT AND ON THE PROCESS OF GASTRIC EVACUATION. J. P. QUIGLEY, M. R. READ, K. H. RADZOW, I. MESCHAN and J. M. WERLE, Am. J. Physiol. **137**:153 (Aug.) 1942.

Employing direct observational methods, the authors obtained evidence that hydrochloric acid in the stomach exerts little or no physiologic action on the motor activities, on the pressure changes in the pyloric sphincter region or on the process of gastric evacuation.

Hydrochloric acid in the duodenum is moderately effective in suppressing the pyloric antrum and thus retards gastric evacuation. The pyloric sphincter and the upper portion of the duodenum are also inhibited, but this is of slight importance in the evacuation process, although some duodenal regurgitation may result if the antrum is more completely inhibited than is the duodenal bulb. Acid in the duodenum may produce a preliminary augmentation of motility in the sphincter region, but in the authors' experience this was of minor importance, since it was rare, transient and moderate.

NOURSE, Cleveland.

NOTES CONCERNING THE CAUSE AND TREATMENT OF CELIAC DISEASE. C. D. MAY, J. F. MCCREARY and K. D. BLACKFAN, J. Pediat. **21**:289 (Sept.) 1942.

Certain laboratory features are consistently found in celiac disease: (1) a low blood sugar curve in the dextrose tolerance test; (2) clumping of the barium sulfate meal in the small intestines because of impaired intestinal motility and a delayed gastric emptying time; (3) defective absorption of fat as evidenced by excess fat in the stools and impaired absorption of vitamin A, and (4) normal pancreatic enzymes as shown by analysis of the duodenal contents.

It was felt of interest to attempt to determine what factor involving the mechanism of fat absorption was at fault. Proper absorption depends on (1) normal intestinal motility, peristalsis and segmentation; (2) emulsification; (3) lipase enzyme action; (4) bile acids; (5) phosphorylation, and (6) normal function of the lymphatic system. Experiments were set up by the authors to test these factors. Results briefly are as follows:

1. Although gastric motility is delayed in celiac disease, correction of this by intraduodenally administered dextrose did not produce a rise in the blood sugar curve.

2. Mecholyl chloride was given to stimulate intestinal peristalsis and segmentation, but no rise in the blood sugar curve occurred when a physiologic solution of 3 per cent dextrose was given intraduodenally.

3. Bile salts plus olive oil and milk as vehicles for vitamin A were given, but no rise in absorption of vitamin A occurred.

4. Bile salts, olive oil and milk plus mecholyl chloride still produced no rise in absorption of vitamin A.

5. Although it is known that pancreatic enzymes are normal in celiac disease, pancreatin was administered, but absorption of vitamin A remained impaired.

6. The lymphatic system must be considered normal, since patients with celiac disease get well and since no abnormality has ever been found at autopsy.

Therefore the authors are led to believe that the fault lies in a failure of the intestinal mucosa itself to absorb fats. They postulate a lack of an intrinsic or extrinsic factor in this condition and note a similarity of the disease to sprue. The possibility of these factors being found in crude liver extracts and crude vitamin B extracts led to their use therapeutically. Two to 4 cc. of crude liver extract (Lilly) given every other day alternating with 2 to 4 cc. of a preparation of vitamin B complex (parenteral B complex Lederle) resulted in great improvement in three to six weeks. These patients responded with rapid gain in weight, improvement in stools, return of normal absorption of vitamin A, rise in the low blood sugar curve and increased intestinal peristalsis and motility. This improvement occurred even when a normal diet was given the child. Attempts are now being made to isolate, if possible, the factor or factors present in liver extract and in vitamin B complex responsible for the cures. To date, however, the crude product is still necessary for recovery, the several isolated factors (nicotinic acid, riboflavin, etc.) have not in themselves been as successful as the crude products containing the full complex.

STETTENBENZ, Buffalo.

VITAMIN A ABSORPTION AND ITS RELATION TO INTESTINAL MOTILITY IN FIBROCYSTIC DISEASE OF THE PANCREAS. LEO J. FLAX, MARIAN BARNES and JOHN L. REICHERT, J. Pediat. **21**:475 (Oct.) 1942.

Flax, Barnes and Reichert report a case of fibrocystic disease of the pancreas in which prostigmine (methylsulfate given parenterally and bromide administered orally) was used to enhance intestinal tone and motility and thus increase the absorption of vitamin A. The response was gratifying, the vitamin A absorption curve showing a satisfactory rise. At the time the paper was written the patient had apparently recovered from the disease. A second sibling of this family, who died shortly after birth, showed cystic fibrosis of the pancreas at autopsy, which bears out the congenital nature of the disease. STETTENBENZ, Buffalo.

LARGE SOLITARY BILE-CELL FIBRO-ADENOMA OF THE LIVER. E. S. LEE, Proc. Roy. Soc. Med. **36**:33 (Nov.) 1942.

The patient, a boy aged 13 months, was taken to the hospital because of abdominal enlargement which had been present at birth. The baby was fretful and seemed to have attacks of abdominal pain. On examination the abdomen was found greatly distended by an enormous tumor. An intravenous pyelogram showed good filling of the left kidney, none of the right. A diagnosis of a Wilms tumor was made, and preoperative roentgen therapy was given without any diminution in size of the tumor; therefore it was decided to operate without further delay. When the abdomen was explored the kidneys were found to be normal, but arising from the inferior surface of the liver was a tumor 8 inches (20 cm.) in diameter. The architecture of the tumor recalled that of a fibroadenoma of the breast. Results of laboratory and clinical investigations, an account of the operation and a description of the tumor are all given in detail in the report. WILLIAMSON, New Orleans.

THE NORMAL STOMACH AND SMALL INTESTINE IN THE INFANT. JOHN S. BOUSLOG, Radiology **39**:253 (Sept.) 1942.

Postmortem macroscopic, microscopic and photographic studies were made of the gastrointestinal tracts of infants who died at birth or shortly thereafter. The necropsy observations were correlated with the results of roentgen examinations of 200 infants.

The first portion of the duodenum is behind the pyloric end of the distended stomach and is not visible in posteroanterior views. The infant must be rotated to the right, to about a 60 degree angle, to show the pylorus and duodenum. The duodenum is like that of the fetus, a more or less short, straight tube, for the first three months. The first portion, as a rule, is in the horizontal position and lies at the level of the first lumbar vertebra. The second and third portions are hard to visualize, probably because of rapid emptying. When they are visualized, they have the same characteristics as the first portion.

In the jejunum and ileum, the barium sulfate test meal does not have the "snow flake" appearance that it has in the adult. It is segmented and grouped. In the first few months of life, the segments vary in size and shape without any definite form. The intestinal wall has a thin, paper-like consistency.

The following histologic observations were made on the fetus:

1. The mucosal folds and valvulae conniventes are more abundant than in the adult, but their length and height are distinctly less.

2. The mucous membrane is absolutely and relatively more developed than the musculature. It is also extremely delicate and vascular and more cellular than that of the adult.

3. Compared with the adult structures, the submucosa is less abundant and more delicate; the elastic fibers are feebly developed.

4. The muscularis develops gradually from a very thin layer to a thickness equal to that of both mucosa and submucosa.

5. The anatomic variations of the mucosa, submucosa and muscularis noted probably explain the segmentation and grouping of the meal in the jejunum and ileum of the infant.

The fetal and infant stomach has lack of muscular development. Rugae are present, and the pylorus is well defined. The stomach corresponds in shape to that of the adult, but in the infant the position is always high. The duodenum appears more like a tube and does not show the divisions of the adult duodenum. The jejunum and the ileum are also less developed than in the adult. The structure of the mucosal folds changes in character at the junction of the jejunum and the ileum in the infant at birth. ANSPACH, Chicago.

THE COLON IN THE HEALTHY NEWBORN INFANT. SAMUEL G. HENDERSON and W. W. BRIANT, Radiology **39**:261 (Sept.) 1942.

This report is based on fluoroscopic and roentgenographic evidence from 105 healthy infants from 2 to 8 days old. Barium sulfate was injected per rectum with the aid of a stopper and manual pressure. Two to 2½ ounces (60 to 75 cc.) of the barium sulfate mixture completely filled the colon.

Defects in mucosal contours were observed rarely and when seen were thought to be due to adherent meconium or feces. Haustrations were nearly always present but more shallow and less numerous than in older infants and adults. In early infancy the sigmoid flexure was always redundant. Similarly, but not always, the descending portion of the colon, the splenic flexure, the transverse portion of the colon, the hepatic flexure and the ascending portion of the colon occupied low positions.

The cecum was at the level of the iliac fossa in 50 per cent of the infants and in 25 per cent at a slightly higher level. The appendix was seen in 23 subjects. This was in contrast to the rarity of visualization after a barium sulfate test meal. The terminal portion of the ileum was easily filled.

Only 19 subjects were observed at later periods, and it was felt that the number was too small to permit conclusions as to subsequent development. The lumen of the colon was seen to be enlarged in infants who had received cathartics as compared with other infants. An unusually large colon was found in several infants who had not received cod liver oil.

Redundancy noted during the first week of life was less marked at the time of later examinations.

ANSPACH, Chicago.

A MILK-BORNE OUTBREAK OF GASTRO-ENTERITIS IN OKLAHOMA CITY. I. M. TERZICH, South. M. J. **35**:773 (Aug.) 1942.

The author reports an outbreak of food poisoning affecting 71 persons in Oklahoma City and surrounding communities in Oklahoma County. The cause of the outbreak is believed to have been a highly contaminated milk supply. The milk had not been properly pasteurized; hemolytic staphylococci and toxin-producing cocci were shown to be present, as were organisms of the Bacillus coli-aerogenes group, and a large amount of neutralizer in the form of carbonates had been added.

The victims of the food poisoning suffered from extremely acute gastroenteritis, but no deaths were reported.

The plant from which the suspected milk supply was obtained employed inadequate pasteurization equipment for the processing of that portion of the milk shipped to Oklahoma City and vicinity. The subsequent contamination of the milk is believed to have been due to an employee with cutaneous eruptions on his hands, arms and face who capped the gallon (3.8 liter) jug containers by hand.

The author believes that the attacks of gastroenteritis were probably due to the ingestion of toxin-producing cocci and hemolytic staphylococci.

SCHLUTZ, Chicago.

TREATMENT OF DIARRHEA IN INFANCY. CHARLES HARRIS, Practitioner **149**:151 (Sept.) 1942.

The author divides the subject into two main divisions: (1) the constitutional disturbances, under which he discusses in detail the treatment of (*a*) collapse; (*b*) dehydration, in treatment of which he advocates subcutaneous infusion, intraperitoneal infusion and intravenous infusion; (*c*) ketosis; (*d*) acidemia; (*e*) uremia; (*f*) loss of proteins, especially to be treated with plasma or whole blood, and (g) general measures. (2) He discusses the second subdivision under the title of "Treatment of Diarrhea Without Dehydration" and finishes the article with a brief summary of chemotherapy in different types of diarrhea.

Most of the diarrheas, he says, will respond to sulfaguanidine, the amount to be given depending on the weight of the infant or child. Good results have been obtained by giving 0.15 Gm. of sulfaguanidine for each kilogram of body weight, the daily dose being divided into four hourly or six hourly portions and continued for three or four days.

THELANDER, San Francisco.

INFECTION AND THERAPY WITH SULFONAMIDE COMPOUNDS IN CASES OF GASTROINTESTINAL DISORDERS AND ENTERITIS OF INFANCY. V. ZERBINO, Arch. de pediat. d. Uruguay **13**:517 (Sept.) 1942.

Infection plays a most important role in gastrointestinal disorders of infancy, whether its location is enteral or parenteral. In most instances of both the severe and the benign acute forms of these disorders the author believes that an intervening infection is the determining

etiologic factor. In the chronic forms the infection is associated with or superimposed on an organism that is wasted and fragile on account of chronic malnutrition. In these cases these infectious agents can produce nutritional crises of a more or less acute type.

In the material the author presents, in 60 to 80 per cent of the cases the infectious agent was of parenteral origin; in 20 to 40 per cent it was enteral. In 50 per cent of the enteral infections the specific enteritis was due largely to two organisms, Shigella and Salmonella. In the other 50 per cent organisms such as Bacillus coli, enterococci, Bacillus proteus, Bacillus of Morgan, Bacillus pyocyaneus, streptococci and staphylococci were the infectious agents. In a few cases spirochetes or a virus seemed to be the main source of infection.

The material of the author included reports on 394 infants between the age of 1 month and 2 years. Three fourths of them were under 1 year of age. All of these infants showed either enteral or parenteral infections. The authors have had excellent success with sulfanilamide therapy in the treatment of enteritis. It is particularly effective in the treatment of Shigella enteritis. In these cases of this disorder the mortality has been reduced to minimal figures, and the course of the disease has been cut short.

The preparations most effective were sulfathiazole, sulfaguanidine and sulfadiazine. The treatment has also been effective for Salmonella enteritis. The best agent for these conditions seems to be sulfathiazole, although the authors had good results with succinylsulfathiazole. The sulfonamide compound used must be diffusible and not limited to local action in the enteritis, because in these cases the enteritis is not a local infection but has a tendency to become general. It is often accompanied by lesions in the pleura and by bronchopneumonia, otitis, sinusitis, degeneration of the liver and adrenal insufficiency.

The author has always found a combination of good dietary measures and chemotherapy an excellent measure and one that gives splendid results. The combined use of these agents will always cut short the disorder or reduce its unfavorable evolution. It is useful in the milder forms of the disorder and prevents these from developing into the more severe types. In the treatment of the dystrophic types it often prevents the severe infections to which patients with these disorders are subject. Vitamins should be given along with the sulfonamide compounds. High doses can be used in the treatment of these infections—0.03 to 0.04 Gm. per kilogram of body weight during the early days of the illness. As long as the diarrhea persists, vomiting may sometimes increase the concentration of the drug in the blood. The treatment is generally well tolerated without general toxic symptoms and can be given to newborn infants, to congenitally debilitated babies and to atrophic infants.

SCHLUTZ, Chicago.

Nervous Diseases

SOME REMARKS ON TUMORS OF THE BRAIN IN CHILDHOOD. OTTO MARBURG, J. Nerv. & Ment. Dis. **95**:446 (April) 1942.

Fourteen to 15 per cent of all tumors of the brain occur in childhood, the climax in the number of cases being in the sixth year. Fifty to 60 per cent of the tumors are found beneath the tentorium in the pontocerebellar region and 30 per cent in the diencephalic area. Of the latter, 25 per cent are found in the vicinity of the base of the hypophysial gland. The pathologic picture and symptoms of the various types of tumors are discussed.

In spite of increasing knowledge of the nature and treatment of tumors of the brain, the prognosis in general remains discouraging.

JAHR, Omaha.

FETAL TOXOPLASMIC ENCEPHALITIS—A TYPE OF CONGENITAL CEREBRAL DISEASE. PAUL M. LEVIN and HALCUIT MOORE, J. Pediat. **21**:673 (Nov.) 1942.

Levin and Moore report a case of fetal toxoplasmic encephalitis presenting the typical clinical picture, of intracranial calcification, chorioretinitis, mental retardation and convulsions. Specific complement-fixing antibodies were demonstrated in the blood of the infant and of the mother.

STETTENBENZ, Buffalo.

THE ANTICONVULSANT ACTION OF DIPHENYL HYDANTOIN AND SOME RELATED COMPOUNDS. P. K. KNOEFEL and G. LEHMANN, J. Pharmacol. & Exper. Therap. **76**:194, 1942.

Experiments were made on cats with convulsions produced electrically after the manner of Putnam. The authors concluded that diphenylhydantoin sodium raises the threshold of electrically produced convulsions in cats. This anticonvulsant activity is not seen in decerebrate cats. Several related compounds were less effective than diphenylhydantoin sodium itself. Attention is called to the fact that this drug does not induce sleep or anesthesia, as pointed out by Putnam.

PILCHER, Cleveland.

OBSERVATIONS ON THE PATHOLOGY OF CEREBRAL DIPLEGIA. R. M. STEWART, Proc. Roy. Soc. Med. **36**:25 (Nov.) 1942.

The author first discusses primary degeneration of the primary neurones, asphyxia and anoxemia; then he gives his report on a study of autopsy material from 50 diplegic aments. In the material there were 50 brains and 30 spinal cords. In his conclusion Stewart states that although much investigation has still to be undertaken, a number of facts stand out sufficiently clearly to justify certain generalizations:

1. There is no evidence in the series of 50 cases of cerebral diplegia of any morbid change in the nervous system which is invariable and specific.

2. It may be observed that the lesions encountered in cerebral diplegia are of characters so diverse as to indicate that the hypothesis of a single cause common to all cases cannot be sustained.

3. The large number of infants born normally at term exhibiting high degrees of microcephally affords clear proof of the prenatal origin of the condition and suggests that birth injury has in the past been assigned far too large a part in the pathogenesis of cerebral diplegia.

4. Many of the lesions encountered in this investigation can best be explained on the basis of Collier's conception of a primary degeneration of the cerebral neurons. The etiologic factors concerned in this degeneration are likely to be numerous. The possibility that anoxemia and nutritional deficiencies are among those concerned deserves serious consideration.

WILLIAMSON, New Orleans.

STUDIES OF THE PHYSICOCHEMICAL RESPIRATORY REGULATION AND THE ACID BASE EQUILIBRIUM IN CHILDREN. H. BRÜHL, Ann. pædiat. **159**:57 (Aug.-Sept.) 1942.

1. In normal infants the carbon dioxide–dissociation curves of the arterial and the venous blood are identical. The venous blood has a higher degree of acidity than the arterial blood, the difference being 0.03 to 0.05 p_H.

2. In high altitudes the curve of the venous blood of the brain (taken from the cerebral sinus) is lower than the arterial curve and the difference between the venous and the arterial p_H is increased to 0.05 to 0.19 (Winterstein and Gollwitzer-Meier). This proves that in consequence of an oxygen deficiency the formation of acids is increased by the metabolism of the brain tissues. The hyperpnea in high altitudes is due to a local acidosis of the respiratory center (Winterstein).

3. Infants with infantile rickets show the same differences between the arterial and the venous carbon dioxide–combining power and p_H as is found in normal infants.

4. But in infantile tetany the difference between the arterial blood and the venous blood of the brain (taken by puncture of the superior longitudinal sinus) is reversed: The venous carbon dioxide–dissociation curve rises over the arterial curve, and the venous blood becomes more alkaline than the arterial.

5. There is a direct proportion between the violence of the tetanic symptoms and the arterial-venous difference: Patients with latent tetanic symptoms have a difference of 2.7 to 5 volumes per cent; patients with laryngospasms, 5.5 volumes per cent; patients with general spasms, 6 to 8 volumes per cent, and patients with general convulsions, 5.7 to 10.7 volumes per cent. The venous blood being always more alkaline than the arterial blood, the arterial-venous difference of the p_H amounts to 0.03 to 0.04 in patients with latent tetanic symptoms and to 0.09 to 0.41 in patients with severe tetanic manifestations.

6. Chemical analyses reveal that in tetany the amount of total fixed base is the same in both the arterial and the venous blood (coming from the brain). Therefore, it seems improbable that the brain has lost any alkali.

7. Furthermore, it was found by electrometric titration (micromethod of Brühl) that the amount of organic acids is lower in the venous blood coming from the brain than in the arterial blood flowing into the brain. This loss of organic anions by the blood passing through the brain corresponds quantitatively to the previously mentioned rise in carbon dioxide–combining power.

8. Normally, organic acids of the blood are kept back by the brain tissues and are transformed by the cerebral metabolism (Gesell, McGinty). In tetany this process is increased. Brühl considers it as a sign of increased irritability of the nerve tissues. The increased output of ammonia found in the spinal fluid of tetanic infants is a symptom of parallel significance.

9. Gesell has proved that increased transformation of organic acid by the cerebral metabolism lowers the carbon dioxide tension in the brain tissues and shifts the reaction of the respiratory center in an alkaline direction. Accordingly low carbon dioxide tension and alkaline p_H were found in the venous blood of the cerebral sinus.

10. This shows that the carbon dioxide tension and the p_H of the blood of the cerebral sinus are significant for the alteration of carbon dioxide tension and p_H in the brain tissues and respiratory center.

11. Normally the venous carbon dioxide pressure is higher than the arterial pressure. In tetany the venous pressure (cerebral sinus) paradoxically falls below the arterial. Haldane has seen this same phenomenon after the carbon dioxide had been given off by the tissues during previous hyperpnea. It is interesting to note that also in tetany a previous hyperpnea was observed.

12. The degree of irritability of the respiratory center is demonstrated by parallel changes of the quotient.

$$QE = \frac{\text{respiration}}{\text{concentration of hydrogen ions}}$$

Normally	$QE = 0.60 - 0.75 \times 10^{11}$	
In latent tetany	$QE = 1.17 \times 10^{11}$	(arterial blood)
	1.29×10^{11}	(venous blood)
In manifest tetany	$QE = 0.70 - 0.80 \times 10^{11}$	(arterial blood)
	$0.85 - 0.99 \times 10^{11}$	(venous blood)
After ultraviolet irradiation	$QE = 0.70 - 0.75 \times 10^{11}$	(arterial blood)
	0.99×10^{11}	(venous blood)
In Cheyne-Stokes respiration	$QE = 0.18 \times 10^{11}$	(arterial blood)
	0.12×10^{11}	(venous blood)

To some extent the p_H of the blood of the cerebral sinus is significant for the p_H of the respiratory center; so the rising of QE demonstrates clearly the increased irritability of the respiratory center in "latent" tetany. In "manifest" tetany and after ultraviolet irradiation an arterial acidosis originating in the periphery of the body spreads over the brain and obscures the cerebral regulatory processes. In spite of that, the characteristic state of the blood in "latent" tetany can also be seen here.

13. Tracings of the respiration taken in manifest tetany and after ultraviolet irradiation reveal that both increased irritability of the respiratory center and acidosis have to be considered as causes of the hyperpnea.

14. In Cheyne-Stokes respiration the carbon dioxide–dissociation curve of the venous blood of the brain falls below the arterial curve, as previously found in high altitudes. An acidosis has been observed in the venous blood and alkalosis in the arterial blood. QE is very low and proves a paralysis of the respiratory center.

15. The carbon dioxide–combining power and the p_H of the blood drawn from the cerebral sinus differ from those of blood from the jugular vein. The carbon dioxide–combining power and p_H of the arterial blood are integrated from the various carbon dioxide contents and p_H's of all types of venous blood.

16. The observations on the blood drawn from the cerebral sinus are significant only for the cerebral metabolism and the reactions of the centers; sometimes they differ widely from the gas-analytic conditions of the rest of the body (as shown in tetany).

[FROM THE AUTHOR'S SUMMARY]

Psychology and Psychiatry

LEARNING TO SPEAK AFTER SIX AND ONE-HALF YEARS OF SILENCE. MARIE K. MASON, J. Speech Disorders **7**:295 (Dec.) 1942.

Mason presents a report of the correction of the speech of a normal but mute child who was imprisoned in solitude with a mute mother for six and one-half years. The article contains a careful description of the technic employed.

PALMER, Wichita, Kan.

A COMPARISON OF THE KINAESTHETIC SENSIBILITY OF SPEECH-DEFECTIVE AND NORMAL-SPEAKING CHILDREN. FRANCES E. PATTON, J. Speech Disorders **7**:305 (Dec.) 1942.

Two hundred and fourteen children with articulatory defects but without hearing losses, cleft palate, cerebral palsy or stuttering were compared with 214 normal children of the same age and sex in regard to their kinesthetic ability on general tests of kinesthesia adapted from Starling. Children with articulatory defects have a lower degree of kinesthesia than normal children.

PALMER, Wichita, Kan.

A Study of Some Social Attitudes of a Group of 59 Stutterers. Spencer F. Brown, J. Speech Disorders **7**:323 (Dec.) 1942.

Fifty-nine stutterers in three midwestern speech clinics had "inferior" speech attitudes and graded significantly "lower" in social adjustment.

Palmer, Wichita, Kan.

An Organized Approach to the Therapy of Stuttering. Stanley Ainsworth, J. Speech Disorders **7**:325 (Dec.) 1942.

The author classifies stutterers into three personality types: (1) those who cannot help stuttering because of neuromuscular involvement; (2) those who stutter because of psychologic maladjustment, and (3) those who stutter because of habit. Ainsworth claims that the proper classification can be easily made by the clinician and that a difference of emphasis in corrective work for each type is important.

Palmer, Wichita, Kan.

A Study of the Relationship Between Stuttering Occurrence and Grammatical Factors in Oral Reading. Eugene F. Hahn, J. Speech Disorders **7**:329 (Dec.) 1942.

Forty-three stutterers read 550 word reading selections in four socially varied situations. Adjectives, nouns and verbs caused more difficulty than other parts of speech. This confirms Brown's earlier study. The agreement of the data is more significant than their variations. A portion of the data can be explained by phonetic factors, but the grammatical factor appears to be much more consistent than the phonetic factor.

Palmer, Wichita, Kan.

Morbid Psychological States Associated with Physical Disabilities. Louis Minski, Brit. J. Phys. Med. **5**:110 (July-Aug.) 1942.

It is not advisable to admit physically disabled children to adult wards or to subject them to fussing and pampering. They should not be given expensive toys and such management as cannot be approximated at home. They should rather be urged to help themselves and each other as early as and as much as possible.

In the case of children permanently crippled it is advisable to send them to special schools for the physically disabled, where they can receive suitable occupational therapy and recreation.

Hartman, Portsmouth, Va.

The Prognostic Factors of Adolescent Psychoses. A. Barham Carter, J. Ment. Sc. **88**:31, 1942.

Carter studied 78 cases of adolescent psychosis. Favorable factors seemed to be some soundness of stock, often associated with a pyknosomatic physique; a helpful environment; severe, acute psychotic episodes, and preservation during the psychosis of "normal," though possibly exaggerated, emotional reactions. On the other hand, an insidious onset, dissociation of emotional reaction, increasing withdrawal from the environment and persistence of symptoms were all indications of a poor prognosis. Particularly unfavorable symptoms were chronic catatonia, stereotypy and grotesque behavior.

Drayer, Philadelphia. [Arch. Neurol. & Psychiat.]

Contribution to the Study of the Relationship Between Infantile Enuresis and Epileptic Crisis. M. Schachter, Ann. pædiat. **159**:19 (July) 1942.

The observation of 36 children with enuresis and subject to epileptic attacks (typical or equivalent) allows the following conclusions to be drawn:

Only few children displaying enuresis have epileptic attacks. We found 7.7 per cent, which accords rather closely with the results of Kanner (Baltimore), who obtained 7 per cent.

These were tainted children. Sixty-one per cent of them were idiots and imbeciles, and only 21 per cent were mentally normal.

For 25 per cent of these children alcoholism of the father was established; about 13 per cent of them had had a malarial infection.

No opinion can be offered as to prognosis, but the author believes that the epileptic attacks persist after enuresis ceases (in 45 per cent of the children observed).

[From the Author's Summary]

Diseases of the Genitourinary Tract

TONSILLECTOMY AND ACUTE NEPHRITIS. JOHN B. LYTTLE, Bull. New York Acad. Med. **18**:356 (May) 1942.

Although the causation of acute nephritis is variable both in the nature of the causative organism and in the specific damage done to the kidney, the author feels that since the throat is the most frequent portal of entry for pathogenic agents any procedure which tends to diminish the occurrence of sore throat may be considered a potential block to the source of danger. For this reason, whenever indications for tonsillectomy exist the tonsils should be removed as a precautionary measure against the development of nephritis.

Nephritis itself, the author states, is not to be considered an indication for tonsillectomy. It is an elective operation, and the time must be decided on in the individual case, preferably when the symptoms and the signs of the acute stage of nephritis have subsided and the pharynx is not acutely inflamed.

JAHR, Omaha.

ACHALASIA OF THE URINARY TRACT IN CHILDREN. J. W. S. LAIDLEY, M. J. Australia **2**:475 (Nov. 28) 1942.

Of the various urinary sphincters, the bladder neck sphincter is the most commonly affected by achalasia. In mild form it will cause frequency of micturition, dysuria or enuresis but not pyuria. Cystoscopic examination reveals trabeculation of the bladder wall as the most important sign. In the next stage of severity, though the bladder wall has hypertrophied still further, it is unable to empty itself completely. At this stage residual urine is present, which sooner or later becomes infected. In the final stage the bladder is atonic and may contain up to a pint of residual urine, which is usually infected. The ureteric orifices become dilated and remain permanently open. Bilateral hydronephrosis rapidly occurs, and signs of early renal failure appear. Less commonly the ureterovesical and rarely the ureteropelvic sphincters may be affected. The diagnosis of achalasia is essentially an exclusion diagnosis. It must not be made unless phimosis, pinpoint meatus, meatitis, congenital urethral structure, hypertrophied verumontanum, median bar and valve of the prostatic portion of the urethra have been excluded in the case of the male patient, and unless small meatus, stenosed meatus, vulvitis, chronic urethritis and small urethra have been excluded in the case of the female patient. In mild forms, in which no structural change has occurred, relief may be given by dilatation of the sphincter involved. With severe involvement the response to any treatment is not favorable. Achalasia is a disease of childhood and persists rarely into adult life, though structural changes caused by it are permanent and last throughout life.

GONCE JR., Madison, Wis.

Diseases of the Ductless Glands; Endocrinology

THE RÔLE OF THE ANTERIOR PITUITARY IN ADRENALINE HYPERGLYCEMIA AND LIVER GLYCOGENOLYSIS. R. C. DEBODO, H. I. BLOCH and I. H. GROSS, Am. J. Physiol. **137**:124 (Aug.) 1942.

DeBodo, Bloch and Gross report that epinephrine hydrochloride infused intravenously at the rate of 0.0035 mg. per kilogram per minute for five minutes produces a pronounced hyperglycemia in normal dogs but the same amount infused at the same rate produces only a slight hyperglycemia in hypophysectomized dogs. This failure of hypophysectomized dogs to respond to epinephrine with a pronounced hyperglycemia occurs despite the presence of ample stores of glycogen in the liver. Fasting normal dogs, with much smaller stores of glycogen in the liver, respond to epinephrine with a far greater hyperglycemia than hypophysectomized animals. Neurohypophysectomized dogs with an intact anterior lobe of the pituitary respond to the hyperglycemic action of epinephrine as normal dogs do. In the absence of the anterior lobe of the pituitary, the glycogen in the liver is less readily mobilized by epinephrine.

[AUTHORS' SUMMARY]

EFFECT OF ADRENAL FACTORS ON PLASMA PROTEINS. FRANK A. HARTMAN, LENA A. LEWIS, JONATHAN S. THATCHER and HAROLD R. STREET, Endocrinology **31**:287 (Sept.) 1942.

The data obtained from experiments on dogs and cats indicate that the adrenal gland is a factor in the maintenance of normal levels of albumin and globulin in the plasma. Without it the albumin falls and the globulin rises. Whole adrenal extract maintained the albumin level but did not prevent the rise in globulin. Therefore it seems that the adrenal extract used did not contain the substance which prevents the rise of globulin.

JACOBSEN, Buffalo.

RELATIONSHIP OF A LOW BLOOD CALCIUM TO PARATHYROID SECRETION. HARVEY M. PATT and ARNO B. LUCKHARDT, Endocrinology **31**:384 (Sept.) 1942.

It is not known whether the parathyroid glands are subject to nervous control, whether they are under the influence of a hormone from the anterior lobe of the hypophysis, or whether there is a local response of the gland cells to chemical changes in the composition of the surrounding fluids.

The experiments on dogs here reported are interpreted as evidence that a low level of calcium in the blood is a direct stimulus to the parathyroid glands to produce more hormone, thus indicating a humoral control of parathyroid secretion. JACOBSEN, Buffalo.

EFFECTS OF HORMONES ON ERYTHROPOIESES IN THE HYPOPHYSECTOMIZED RAT. ERWIN P. VOLLMER, ALBERT S. GORDON and HARRY A. CHARIPPER, Endocrinology **31**:619 (Dec.) 1942.

Thyroxin causes changes in the blood picture of hypophysectomized animals resembling the changes brought about by testosterone, i. e., noticeably increased erythrocyte count, slightly increased hemoglobin level, reticulocytosis and repair of the bone marrow. Prolactin produces similar but less pronounced alterations. Desoxycorticosterone acetate maintains the red cell count and hemoglobin level above those of untreated hypophysectomized rats without bringing about repair of the marrow. JACOBSEN, Buffalo.

ADRENAL CORTICAL HYPERPLASIA WITH VIRILISM: DIAGNOSIS, COURSE AND TREATMENT. NATHAN B. TALBOT, ALLAN M. BUTLER and R. A. BERMAN, J. Clin. Investigation **21**:559 (Sept.) 1942.

The total urinary excretion of 17-keto steroids is abnormally increased in patients with adrenal cortical hyperplasia or adrenal cortical carcinoma. However, the total excretion of 17-keto steroids is not always a reliable index of the exact nature of this hyperactivity. On the other hand, the urinary output of the beta-alcoholic and the nonalcoholic 17-keto steroids has been found to be greatly elevated in patients with adrenal cortical carcinoma whereas the output of these fractions was either normal or but slightly elevated in patients with cortical hyperplasia. Assay of the excretion of the latter two fractions therefore appears to be of diagnostic value in the differentiation of adrenal cortical hyperplasia from carcinoma of the adrenal cortex. [AUTHORS' SUMMARY]

ANTAGONISM OF PITRESSIN AND ADRENAL CORTICAL EXTRACT IN HUMAN DIABETES INSIPIDUS. JOHN A. ANDERSON and WILLIAM R. MURLIN, J. Pediat. **21**:236 (Sept.) 1942.

Animal experimentation has clearly shown the antagonistic effects of pitressin and adrenal cortex extract, the administration of the latter producing polyuria similar to that observed in diabetes insipidus. Injection of pitressin checked the polyuria. Similar studies were made on a 9 year old boy suffering from severe diabetes insipidus, and the antagonistic action of the two substances was satisfactorily demonstrated. One finding of interest was the fact that adrenal cortex extract was unable to produce increased excretion of potassium unless pitressin was supplied. STETTENBENZ, Buffalo.

LAURENCE-MOON-BIEDL SYNDROME: A REPORT OF TWO CASES WITH UNUSUAL COMBINATIONS OF HEREDOFAMILIAL DEVIATIONS. LOUIS A. LURIE and SOL LEVY, J. Pediat. **21**:793 (Dec.) 1942.

The case of a boy aged 13½ years and that of a girl aged 20 years, each presenting a combination of obesity, genital dystrophy, dwarfism, mental retardation and syndactyly with indications of familial occurrence have been thoroughly studied by the authors. Retinitis pigmentosa was the only cardinal symptom of the Laurence-Moon-Biedl syndrome lacking. In addition, eighth nerve deafness was present in both subjects, a rather unusual combination. A laboratory finding of particular interest in the case of the boy was the low value for excretion of 17-keto steroids, and in the case of the girl estrogen deficiency was indicated by the history of delayed onset of menstruation, by its irregularity and by the extremely scanty flow. Electroencephalograms also were done, and in the case of the boy they revealed definite cerebral dysrhythmia. The authors point out that the syndrome is not a progressive disorder but a combination of many heredofamilial deviations. The condition must be differentiated from juvenile familial amaurotic idiocy, Schüller-Christian disease, juvenile dementia paralytica and cerebral sclerosis of Scholz. STETTENBENZ, Buffalo.

Skin Diseases; Allergy

ABSORPTION OF ALLERGENS. MATTHEW WALZER, J. Allergy **13**:554 (Sept.) 1942.

In his address the author presented the results of a series of investigations extending over a period of years dealing with the absorption of proteins. He emphasized "the fact that the absorption of unaltered protein into the circulation is a normal, physiologic phenomenon occurring in nonatopic as well as atopic individuals, at all ages, and with many allergens. The facts concerning this absorption must be taken into consideration in the evaluation of theories of food sensitization. Keeping them in mind should also be of some assistance in the practical management of allergic illnesses."

This is an interesting article showing that proteins are absorbed from many surfaces.

HOYER, Cincinnati.

STUDIES IN FOOD ALLERGY: II. SENSITIZATION TO FRESH FRUITS: CLINICAL AND EXPERIMENTAL OBSERVATIONS. LOUIS TUFT and GEORGE I. BLUMSTEIN, J. Allergy **13**:574 (Sept.) 1942.

Through observations on 4 persons showing reactions to fresh fruits but not to canned or stewed fruits the authors demonstrated a labile antigen in fresh fruit extracts. Deterioration of the antigen is rapid, especially in the first twenty-four hours, and is complete in three days. It is either altered or destroyed in the process of stewing or canning the fruit. Rapid freezing seems to preserve it. The lability of this antigen in fresh fruit probably accounts for the failure to get positive cutaneous reactions in clinically sensitive patients.

HOYER, Cincinnati.

ALLERGY IN IDENTICAL TWINS: REPORT OF SEVEN PAIRS OF TWINS. LEO H. CRIEP, J. Allergy **13**:591 (Sept.) 1942.

"These reports emphasize the following:

"A. The similarities in allergic manifestations in identical twins.

"B. The marked constitutional tendencies towards the development of allergic conditions in each.

"C. Occasional slight differences which may be explained by minor variations in exposure and contact."

The discussion following the paper brought out the fact that it is extremely difficult to determine whether twins are identical. Finger prints are probably the surest indications, since the finger prints of one twin are the mirror image of those of the other.

HOYER, Cincinnati.

THE TREATMENT OF RHUS POISONING BY ALCOHOLIC EXTRACTS IN A SMALL GROUP CONTROLLED BY PRELIMINARY PATCH TESTS. J. R. CLARKE JR. and C. M. HANNA, J. Allergy **13**:599 (Sept.) 1942.

The study was made on a group of 82 boys in camp. Preliminary patch tests were made on the group, an alcoholic extract in dilutions of 1:500 or 1:100 being used.

The authors feel that prophylactic injections of an alcoholic extract gave satisfactory results. No member of the group was incapacitated by Rhus dermatitis, and there was no pruritus ani or perianal dermatitis.

HOYER, Cincinnati.

ORAL PROPHYLAXIS AGAINST POISON IVY: FOLLOW-UP REPORT. HERMAN GOLD and PETER MASUCCI, J. Allergy **13**:606 (Sept.) 1942.

A tablet containing the oleoresin of Rhus toxicodendron was used in the study.

"The incidence of toxic skin reactions was high, and the desensitization obtained appears to be of rather short duration, lasting in some patients only a few months."

HOYER, Cincinnati.

BODY FATS IN RAT ACRODYNIA. F. W. QUACKENBUSH and H. STEENBOCK, J. Nutrition **24**:393 (Oct.) 1942.

Quackenbush and Steenbock in their recent work on acrodynia in rats found the crude fatty acids decreased in amount but increased in iodine number during the development of acrodynia on a low fat diet. There were no significant alterations in the quality or quantity of fat with the noncurative single supplements, pyridoxine and pantothenic acid. Linoleic

ester, rice bran concentrate or pyridoxine plus pantothenic acid, supplements which cured or alleviated the dermal symptoms, produced increased total fat and decreased iodine number. They also found that the fatty acids from acrodynic rats or from rats cured with rice bran concentrate did not cure acrodynia; thus it was apparent that little storage of essential acids had been effected by the rats during the production of acrodynia and that no marked synthesis had resulted from the ingestion of rice bran concentrate. FREDEEN, Kansas City, Mo.

A SERIES OF SUBSTITUTES FOR MILK IN THE TREATMENT OF ALLERGIES. LEON Z. WOLPE and PAUL C. SILVERSTONE, J. Pediat. **21**:635 (Nov.) 1942.

This paper deals with a number of milk substitutes given to infants allergic to cow's milk. Nine varieties of flour were used as bases for milk substitutes: namely, oat, barley, soy, lima bean, pea, taro, rice, rye and corn. These were prepared in formula form by the addition of oil (cottonseed, olive, sesame, corn, peanut or soy), imitation vanilla, dicalcium phosphate, 10 per cent aqueous solution of ferric chloride, saccharin and vitamins in powder form. The formulas were not difficult to prepare, as evidenced by the fact that the mothers cooperated well. They were taken well by the infants, and gain in weight and development were satisfactory. Babies found to be allergic to milk in any form, and that includes milk boiled for one hour, evaporated and dried milks and goat's milk, were fed the experimental formulas, and results were good, the rashes clearing in a few days' time. Other measures included the establishment of a dust-free sleeping room and appropriate local therapy to the lesions.

The authors believe their formulas to be better than the standard fixed milk substitutes (usually containing soybean) on the market, for in their preparation there is great flexibility and a chance is provided to alter the formula to suit the individual baby's needs and tastes.

STETTENBENZ, Buffalo.

AN IN-VIVO METHOD FOR THE EVALUATION OF GERMICIDAL SUBSTANCES USED FOR SKIN DISINFECTION. RAYMOND W. SARBER, J. Pharmacol. & Exper. **75**:277 (July) 1942.

The method consisted of applying organisms capable of causing a fatal peritonitis to the abraded skin of white mice, painting the disinfectant over this area and after a suitable time transferring the area of skin to the peritoneal cavity. If the germicide was effective, the mouse lived; if not, a fatal peritonitis developed. Tincture of iodine was most effective of a group of four drugs tested, but 1 of 5 mice died. Of the three nonirritating germicides, the order of efficiency (in ascending order) was cetylpyridinium chloride (1:200 tincture), sodium ethylmercurithiosalicylate (1:1,000 tincture) and hexylresorcinol (1:1,000 aqueous solution), the last-named compound being about as efficient as iodine.

Evidence has been advanced to support the theory that the skin has a definite bactericidal power which it may exert in combination with chemicals, so that the two together may overcome a bacterial invasion or infection that neither the skin alone nor the germicide alone was able to do in the experimental work. PILCHER, Cleveland.

CONGENITAL ICHTHYOSIS. E. PELUFFO and P. F. BERRUTI, Arch. de pediat. d. Uruguay **13**:378 (Aug.) 1942.

The authors describe congenital ichthyosis in a premature infant. This rare condition was not present in either the father or the mother.

The infant weighed 1,900 Gm. and showed extreme dryness of the skin and complete absence of hair and nails. The temperature was subnormal. The respiration was superficially irregular. There was muscular hypotonia.

The infant died on the thirty-fifth day of life. No treatment had any effect on the condition.

SCHLUTZ, Chicago.

Teeth and Dentistry

DOMESTIC WATER AND DENTAL CARIES. H. T. DEAN, F. A. ARNOLD JR., E. ELVOVE, DAVID C. JOHNSTON and E. M. SHORT, Pub. Health Rep. **57**:1155 (Aug. 7) 1942.

The subjects of this study included 7,257 white school children between the ages of 12 to 14 years from twenty-one cities. They were all children who had been exposed to the common water supply throughout life. A general inverse correlation between the fluoride concentrations of the public water supplies in the twenty-one cities studied was observed. Low prevalence of dental caries was found associated with use of domestic waters the fluoride content of which was as low as one part per million. As in previous studies marked differences were observed with respect to (*a*) the amount of dental caries in the proximal surfaces of the

four superior permanent incisors and (*b*) the mortality rates of the first permanent molars. The authors assume that differences in the first molar mortality rates are influenced to a considerable degree by a variation in either the intensity of the attack of dental caries and/or the resistance of the teeth to the attack.

SANFORD, Chicago.

Miscellaneous

POSSIBLE HAZARDS OF REPEATED FLUOROSCOPIES IN INFANTS. FRANZ BUSCHKE and H. M. PARKER, J. Pediat. **21**:524 (Oct.) 1942.

This paper is a warning against indiscriminate use of the fluoroscope, particularly when physicians routinely include a fluoroscopic examination of infants in their monthly examinations. The inherent dangers lie in possible damage to the skin, hemopoietic system, epiphyses of the growing bones and gonads from the radiation.

The authors believe that because of the small dose little damage could occur to the skin, the hemopoietic system and the epiphyses, but they feel that irradiation of the gonads may affect germ plasm. Damage here may not be revealed in the infant examined, but the possibility exists that detrimental effects on future generations through altered germ plasm may occur.

STETTENBENZ, Buffalo.

PLASMA PROTHROMBIN AND LIVER FUNCTION DURING SULFONAMIDE THERAPY. ISRAEL KAPNICK, JOHN D. STEWART and CHAMP LYONS, New England J. Med. **227**:944 (Dec. 17) 1942.

Hepatic function, as measured by the prothrombin, van den Bergh and bromsulphalein tests, was measured in 68 patients receiving a sulfonamide compound for an acute infection. Fourteen patients, or 21 per cent, showed a significant decrease in the prothrombin level during chemotherapy. The severity of the infection seemed to be more significant as the cause of depression of the prothrombin level than did the type of sulfonamide compound used. Inasmuch as serious infection and sulfonamide drugs are both prejudicial to the welfare of the liver, it seems wise to recommend some test of hepatic function as a routine procedure whenever a sulfonamide compound is used in treatment of an acute infection.

The Quick method of determining the plasma prothrombin level is simply and easily performed and is relatively inexpensive. It is suggested that prothrombin determinations by this method be done every three days in seriously ill patients receiving a sulfonamide compound.

GENGENBACH, Denver.

ABSORPTION AND EXCRETION OF SULFAMETHYLDIAZINE (2-SULFANILAMIDO-4-METHYL-PYRIMIDINE) IN HUMAN SUBJECTS. ROBERT A. GOODWIN JR., OSLER L. PETERSON and MAXWELL FINLAND, Proc. Soc. Exper. Biol. & Med. **51**:262 (Nov.) 1942.

Sulfamethyldiazine was given as a single 5 Gm. dose to 3 human subjects, and blood levels and urinary excretions were compared with those found in 11 subjects who were given similar amounts of sulfadiazine. The concentration of sulfamethyldiazine in the blood rose more rapidly, reached twice the concentration and remained high longer than that obtained with sulfadiazine. From 84 to 100 per cent of the sulfamethyldiazine was recovered from the urine, while from 51 to 61 per cent was recovered as conjugated (acetylated?) in the first twenty-four hours and 56 to 69 per cent of the drug recovered during the next forty-eight hours was in the conjugated form. With sulfadiazine the average urinary recoveries were 52 to 81 per cent respectively for the first twenty-four to seventy-two hours respectively, and 26 to 35 per cent of drug was in the conjugated form during the first twenty-four and the next forty-eight hours respectively. The higher blood levels and the greater solubility offer the possibility of less irritation to the urinary tract from precipitated crystals. The authors believe that sulfamethyldiazine deserves a clinical trial with doses that are smaller than those customarily used. Particular attention should be paid to the possibility of renal or nerve damage if prolonged treatment with the drug is contemplated.

HANSEN, Minneapolis.

CANCER IN CHILDHOOD. MAX RITVO, JOHN D. HOUGHTON and EUGENE J. MCDONALD, Radiology **39**:278 (Sept.) 1942.

Of 153,846 persons dying of cancer in the United States in 1939, 1,103, or 0.7 per cent, were under 15 years of age.

During the year 1939 there were in Massachusetts more childhood deaths from cancer than from any of the following diseases: pertussis, pulmonary tuberculosis, measles, diabetes, cerebrospinal meningitis, syphilis, scarlet fever and typhoid.

A statistical study has been made of all malignant neoplasms in children from birth through 15 years of age observed at the Boston City Hospital for the twenty-five year period from 1915 to 1939, inclusive. In this study a total of 72 cases were collected. The largest

group was the cases of intracranial neoplasms, which numbered 23, or 32 per cent of the entire series. Cases of tumors of the kidney comprised the second largest group, numbering 13, or 18 per cent.

During the same twenty-five year period, there occurred 11 cases of Hodgkin's disease (other than sarcoma) and 27 of leukemia.

The commonest tumors were glioma (medulloblastoma, astrocytoma and mixed glioma), Wilms's tumor, osteogenic and Ewing's sarcoma and miscellaneous soft tissue sarcomas. There were 3 carcinomas of the adult type.

The relatively small number of neuroblastomas of the adrenal is in marked contrast to the findings in previously reported series.

Among the earliest cancers were a Wilms tumor at 1 year, a medulloblastoma at 1 and at 2 years and a fibrosarcoma at 2 years.

The only congenital tumor in the series was a malignant teratoma of the orbital region.

ANSPACH, Chicago.

DISEASES OF CHILDREN. ALAN MONCRIEFF, Practitioner **149**:216 (Oct.) 1942.

The author reviews the recent literature on diseases of children under the following heads:

1. *Asphyxia Neonatorum.*—He comments on the roentgen studies of thoracic circulation, which indicate that the ductus arteriosus closes abruptly when the cord is tied, and states that this is an argument for tying the cord promptly rather than delaying, waiting for pulsation to cease. The argument for delay is that if this is not done anemia may occur. He believes that the closing of the ductus arteriosus is more important.

2. *Vitamin K and Neonatal Hemorrhage.*—He points out that not all hemorrhages in the newborn are due to low levels of prothrombin in the plasma and that vitamin K will not help all types of hemorrhage in the newborn.

3. *Icterus Gravis Neonatorum.*—Here he mentions the "rhesus factor" and briefly reviews the more recent work on this problem.

4. *Diphtheria Prophylaxis.*—This section contains nothing new to American physicians.

5. *Celiac Disease.*—A short summary of celiac disease is given, in which the author particularly mentions the vitamins and more particularly the vitamin B complex.

6. *Respiratory Disorders.*—Under this heading he deals with the treatment of acute bronchiolitis, in which is recommended moist air with an adequate supply of oxygen, chemotherapy and aspiration when necessary.

7. *Cretinism.*—This section includes a discussion of the mental status as influenced by treatment.

8. *Threadworms.*—The author describes the cellophane swab that is in use.

THELANDER, San Francisco.

THE EIGHTH PAN-AMERICAN CHILD CONGRESS: ITS PROJECTION IN AMERICA. VICTOR ESCARDÓ Y ANAYA, Bol. Inst. internac. am. de protec. a la infancia **16**:280 (Oct.) 1942.

The author refers to the development attained in child protection in the different American countries during the last seven years. This is demonstrated by the foundation or reorganization of different establishments and by the promulgation of laws in behalf of mothers and children.

In some municipalities and rural areas protection is carried out by local resources and in others by national subsidies. The supervision of health of mothers and children has been coordinated with general public health; this has brought great benefits. Prenuptial examination has been extended, and prenatal care acquires new and concrete forms. Maternity hospitals and services for the protection of infants and the extension of breast feeding have been improved. In relation to preschool children less is known. Protection of school children is constantly being better organized, and so is nutrition for mothers and children, for in the different countries agencies have been established for that special purpose. The development in medical care is also important. At present there are more hospitals for children and the number of beds has been increased; special attention is now given to syphilis and tuberculosis.

Statistics should be completed and improved; they show in general a decrease in infant mortality. The training of skilful personnel is at present the worry of the various countries. The author finally states that the enumeration is possibly not complete and asks of pediatricians and child welfare workers data for better information. [EDITOR'S SUMMARY]

News and Comment

GENERAL NEWS

American Board of Pediatrics, Inc.—The American Board of Pediatrics, wishing to take cognizance of the present nature of wartime opportunities for young physicians seeking hospital experience, has ruled that three periods of nine months of graduate training shall constitute acceptable training instead of the three full years of training previously required. Two of the periods of nine months must be spent in a pediatric center, or a part of the period not to exceed six months must be spent in a recognized hospital for the care of persons with contagious diseases. This ruling may be applied only in those instances in which the shorter periods of training were the direct result of the present wartime hospital programs for interns and residents.

In issuing the foregoing ruling the board is forced to point out that the pressure of emergency conditions can in no way be allowed to lower the standards of its examination. It is contemplated that many candidates will find it necessary to seek additional postgraduate training after the war in order to be prepared properly for the examination.

The board has decided to reopen group I, the requirement for which is that an applicant shall have been specializing in pediatrics for ten years or more, until July 1, 1944. After this date, this group will be abolished and all applicants will be required to fulfil the minimum requirement of three years (or three periods of nine months, as specified in the preceding pargraphs) of hospital training two years of which is pediatric.

Children's Memorial Hospital, Chicago.—It has been officially announced that beginning Jan. 1, 1944, Dr. Stanley Gibson will be physician in chief and Dr. John A. Bigler assistant physician in chief and medical director of the Children's Memorial Hospital, 707 West Fullerton Avenue, Chicago.

PERSONAL NEWS

New Appointment for Dr. Harvey F. Garrison.—Dr. Harvey F. Garrison, Jackson, Miss., has been appointed a member of the Advisory Committee to the Children's Bureau of the United States Department of Labor, Washington, D. C.

Book Reviews

Creatine and Creatinine Metabolism. By Howard H. Beard, Ph.D. Price, $4.00. Pp. 376, with 50 tables. Brooklyn: Chemical Publishing Co., Inc., 1943.

This monograph attempts to bring up to date the available information which was accumulated since Hunter published his excellent monograph on the same subject in 1926. Included in the present volume are chapters on the determination, distribution, origin and excretion of creatine and creatinine. Other chapters deal with the relation between these substances and water, energy, mineral and carbohydrate metabolism, as well as between them and the hormones.

Although the present monograph is reasonably complete with respect to bibliography and subject matter, it is found lacking in certain other respects. The author displays a lack of understanding of several of the physiologic processes which he discusses and appears to have taken a biased point of view on others. For these reasons it is difficult to recommend the present volume to the student who is seeking a scholarly appraisal of the present knowledge of creatine and creatinine metabolism. However, the book should prove useful to the investigator as a source of data and references.

Behind the Sulfa Drugs. By Iago Goldston, M.D. Price, $2.00. Pp. 174, with no illustrations. Brooklyn: D. Appleton-Century Company, Inc., 1943.

This small book, which was written for the layman, is educational and yet as interesting to read as a novel. Without sensationalism Dr. Goldston tells the story of the development of ancient and modern drug therapy from plant to chemical agents. For two thousand years drugs were entirely of plant origin; for the past four hundred years research has been carried on in the search for chemical drugs which could be used in the treatment of the diseases of man. It has been only within the last ten years that the sulfonamide drugs, the most successful of these chemical agents, have been developed. They represent medicine's greatest victory over infectious diseases. The courage and inspiration, the frustration and disappointment and the success which was finally achieved by the men who played a part in their development is told. This is a nontechnical story which the layman should know and from which medical students can get inspiration.

Tables of Food Values. By Alice V. Bradley, M.S. Price, $3.50. Pp. 224, with no illustrations. Peoria, Ill: Manual Arts Press, 1943.

This very complete set of food tables with instructions as to their use should prove valuable at present, with food rationing and shortages in various staples. The book is well organized and has a complete index.